3.3.1.2. *Measured Exposures to ETS-Associated Nicotine and RSP*

3.3.1.2.1. *Measurements using stationary monitors.* In the past several years, numerous studies have been conducted in a variety of indoor environments to determine the impact of tobacco combustion on levels of nicotine and RSP. These studies have employed a variety of protocols that used a diversity of air sampling techniques (passive, active, continuous integrative, etc.), sampled over highly varying timeframes (from minutes to several days), and collected highly variable information on factors affecting the measured concentrations (number of cigarettes smoked, volume of building, ventilation rates, etc.). In an attempt to present an overall view of the contribution of ETS to indoor air quality, only the summary results of the measured concentrations of ETS-associated nicotine and RSP will be discussed here. Several reviews of the studies evaluating the impact of ETS on indoor RSP levels have been conducted over the past few years, and a number of recent reports have discussed measured indoor levels of nicotine (e.g., NRC, 1986; U.S. DHHS, 1986; Guerin et al., [redacted]). Only the indoor levels measured are discussed and summarized. In order to assess exposures, the time in contact with the concentrations would have to be estimated or measured. The reader is referred to those reports and to the individual study reports to acquire more detailed information.

Measured nicotine concentrations in various indoor environments where smoking was noted are summarized in Figure 3-4. The mean concentration, standard deviation, and the maximum and minimum values recorded are presented. Also given in Figure 3-4 are the number of locations in which the measurements were taken and the references in which the data were reported. Elevated nicotine levels were measured in all microenvironments in which smoking was reported. Measured nicotine levels, as would be expected, were highly variable, covering several orders of magnitude.

The home and workplace may represent the most important environments for exposure to ETS because of the amount of time individuals spend there. For the five studies reporting residential levels, average nicotine concentrations in homes where smoking occurs ranged from less than 1 $\mu g/m^3$ (Leaderer and Hammond, 1991) to over 14 $\mu g/m^3$ (Muramatsu et al., 1984). For two of the studies (Leaderer and Hammond, 1991; Marbury et al., 1990) nicotine concentrations represent weekly averages. Actual concentrations in the homes during nonsleeping occupancy (i.e., while smoking would be occurring) would be considerably higher than the levels presented in the table (a factor of 3 or more higher). Workplace nicotine also demonstrated a wide range of concentrations, from near zero to over 33 $\mu g/m^3$. In other environments, nicotine concentrations also demonstrated considerable variability. It is important to note that short-term concentrations

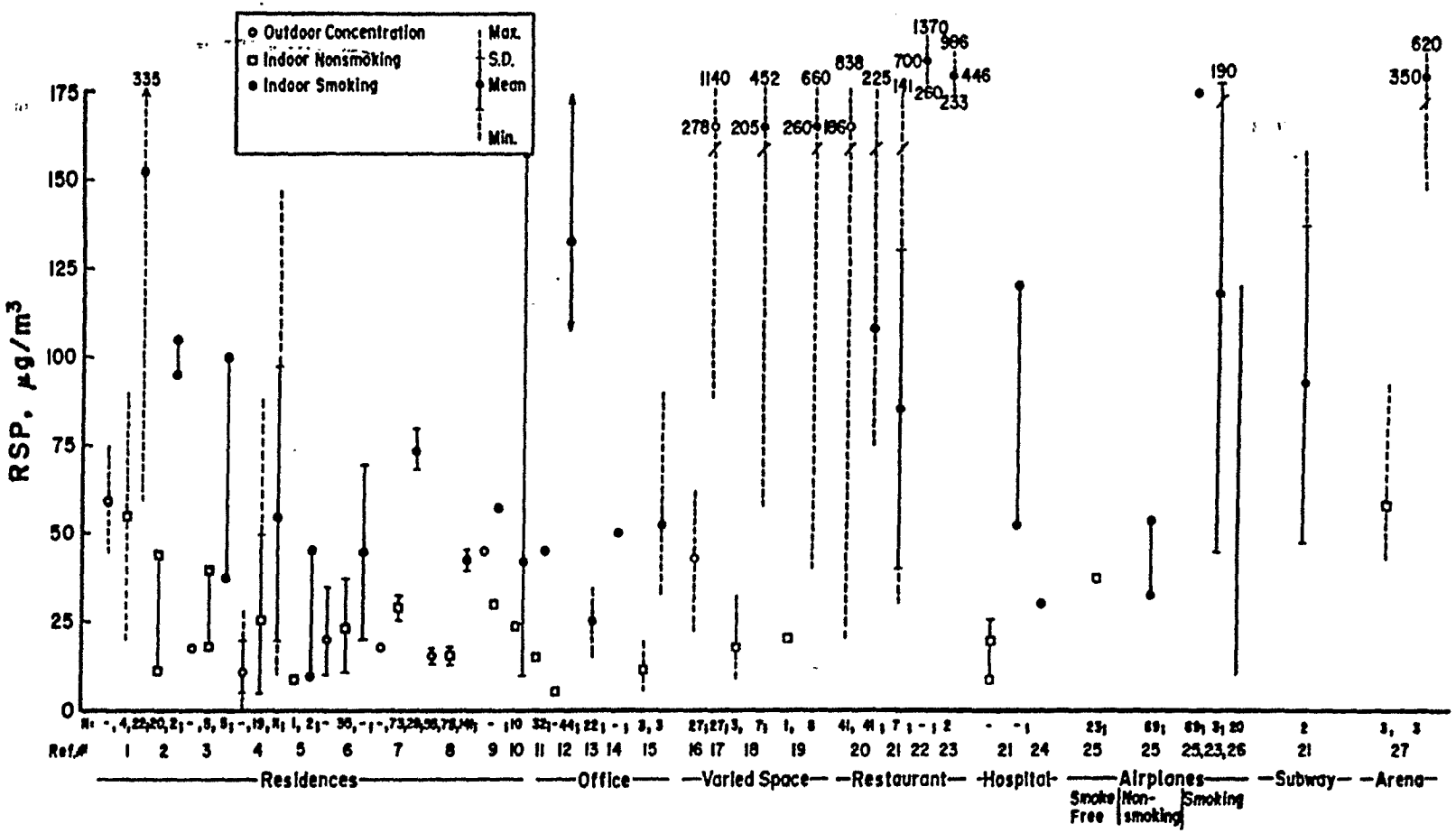

Figure 3-4. Mean, standard deviation, and maximum and minimum nicotine values measured in different indoor environments with smoking occupancy. References from which observations are reported and the number of environments monitored are also given.

REFERENCES FOR FIGURES 3-4 AND 3-5

Figure 3-4

1. Leaderer and Hammond, 1991
2. Mumford et al., 1989
3. Marbury et al., 1990
4. Muramatsu et al., 1984
5. Coultas et al., 1990b
6. Weber and Fischer, 1980
7. Vaughan and Hammond, 1990
8. Leaderer, 1989
9. Miesner et al., 1989
10. Hinds and First, 1975
11. Oldaker et al., 1990
12. Coghlin et al., 1989
13. Badre et al., 1978
14. Higgins, 1987
15. Nagda et al., 1990
16. Eatough et al., 1990
17. Mattson et al., 1989
18. Harmsden and Effenberger, 1957
19. Cano et al., 1970

Figure 3-5

1. Brunekreef and Boleij, 1982
2. Hawthorne et al., 1984
3. Moschandreas, 1981
4. Nitschke et al., 1985
5. Parker et al., 1984
6. Spengler et al., 1981
7. Spengler et al., 1985
8. Leaderer et al., 1990
9. Lebret et al., 1990
10. Coultas et al., 1990b
11. Turk et al., 1987
12. Weber and Fischer, 1980
13. Sterling and Sterling, 1983
14. Nelson et al., 1982
15. Quant et al., 1982
16. Repace and Lowery, 1980
17. Repace and Lowery, 1982
18. Leaderer, 1989
19. First, 1984
20. Oldaker et al., 1990
21. Ishizu, 1980
22. Husgafvel-Pursiainen et al., 1986
23. Eatough et al., 1990
24. Neal et al., 1978
25. Nagda et al., 1990
26. U.S. Department of Transportation, 1971
27. Elliot and Rowe, 1975

(on the order of minutes) are likely to show considerably more variability, resulting in considerably higher short-term peak exposures.

A substantial number of studies examining the impact of tobacco combustion on concentrations of RSP in various indoor environments have been reported. Many of these studies have reported outdoor RSP concentrations and indoor RSP levels without smoking as well as concentrations when smoking occurs. These studies are summarized in Figure 3-5. Outdoor and indoor RSP levels for each of the studies as well as the smoking-associated RSP measurements are shown. The sampling time for the presented data ranged from one minute to over several days. A major portion of the data is for the residential indoor environment. Where smoking is reported, RSP levels are considerably higher than RSP levels outdoors or indoors without smoking. RSP levels associated with smoking, like those for nicotine, demonstrated considerable variability ranging from a few $\mu g/m^3$ to over 1 mg/m^3. Workplace RSP levels associated with smoking occupancy are comparable to residential RSP levels.

In one large residential study, both ETS-associated nicotine and RSP levels were found to be highly correlated ($r = 0.84$; $p < 10^{-5}$) with reported number of cigarettes smoked (Leaderer and Hammond, 1991). This study found that, consistent with chamber data, measured nicotine concentrations predicted the contribution to residential RSP levels from tobacco combustion (Figure 3-6). The data in Figure 3-6 might be used to estimate the RSP levels associated with tobacco combustion from the nicotine levels shown in Figure 3-4. The predictive equation, along with the standard errors, is given in the figure and figure legend. In a study of the impact of smoking on residential levels of RSP and nicotine and of urinary cotinine levels in nonsmoking occupants involving 10 homes, a correlation of 0.54 between residential levels of RSP and nicotine was found (Coultas et al., 1990b).

Indoor levels of nicotine and RSP associated with the combustion of tobacco are a function of several factors related to the generation, dispersal, and removal of ETS in enclosed environments (see Section 3.3.1). Thus, measured levels of these air contaminants indicate a wide range of concentrations (Figures 3-1 and 3-2). Figures 3-7 and 3-8 present a summary of the range of nicotine and ETS-associated particle concentrations measured by type of environment. The figures present the range of average values reported for each study and the minimum and maximum values reported. Only studies reporting sampling times over 4 hours were included in the residential and office summaries in Figures 3-7 and 3-8, because the averaging time is more likely to represent the exposures associated with occupancy time (this included most of the studies for residential spaces shown in Figures 3-4 and 3-5). Since occupancy time in other environments (e.g., restaurants) is likely to be much shorter, averaging times on the order of minutes or greater were considered for the other indoor environments presented in the figures. Indoor particulate

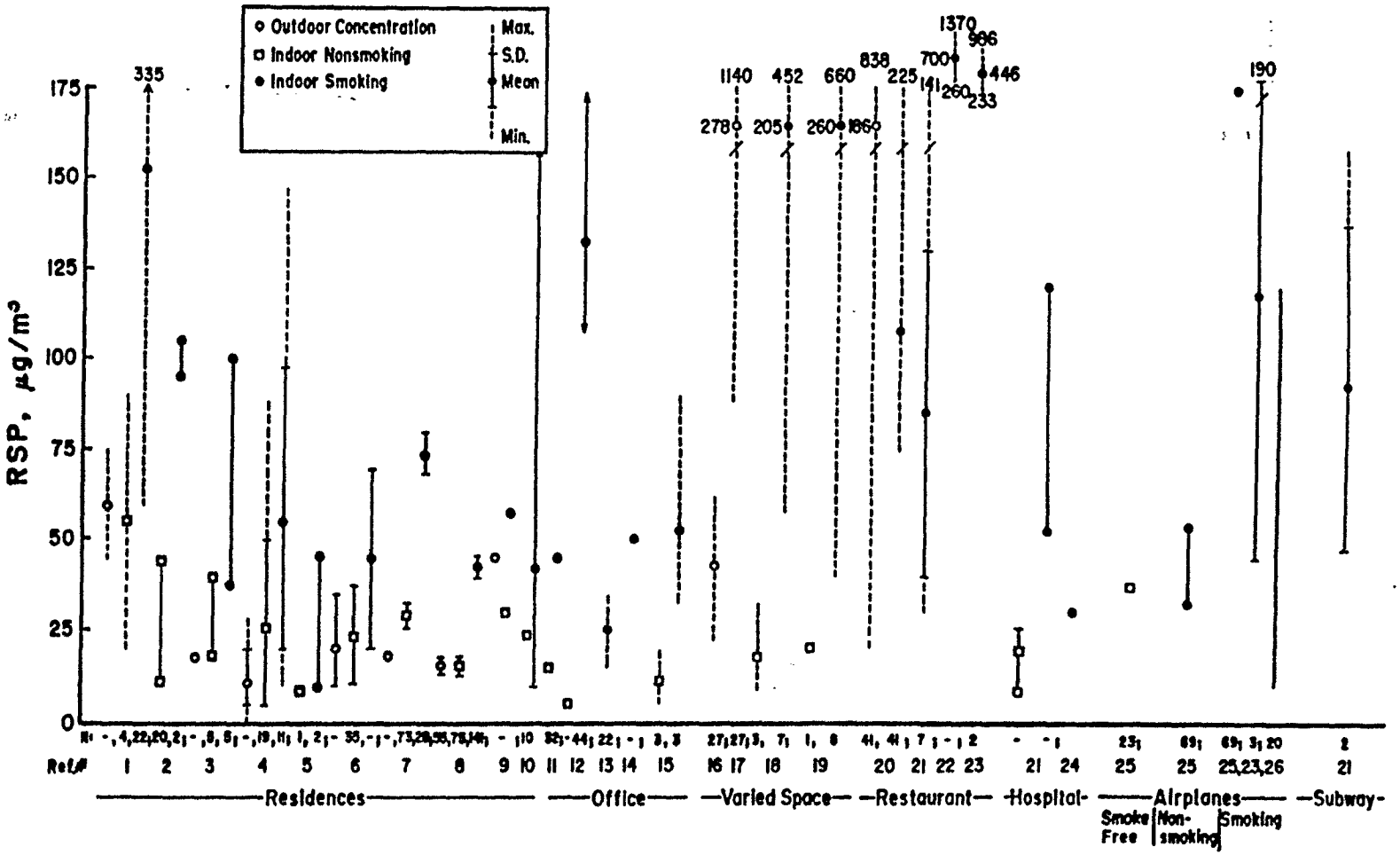

Figure 3-5. Mean, standard deviations, and maximum and minimum concentrations of respirable suspended particle mass (RSP) measured in different indoor environments for smoking and nonsmoking occupancy. Also shown are outdoor concentrations. References from which observations are reported and the number of environments monitored are also given.

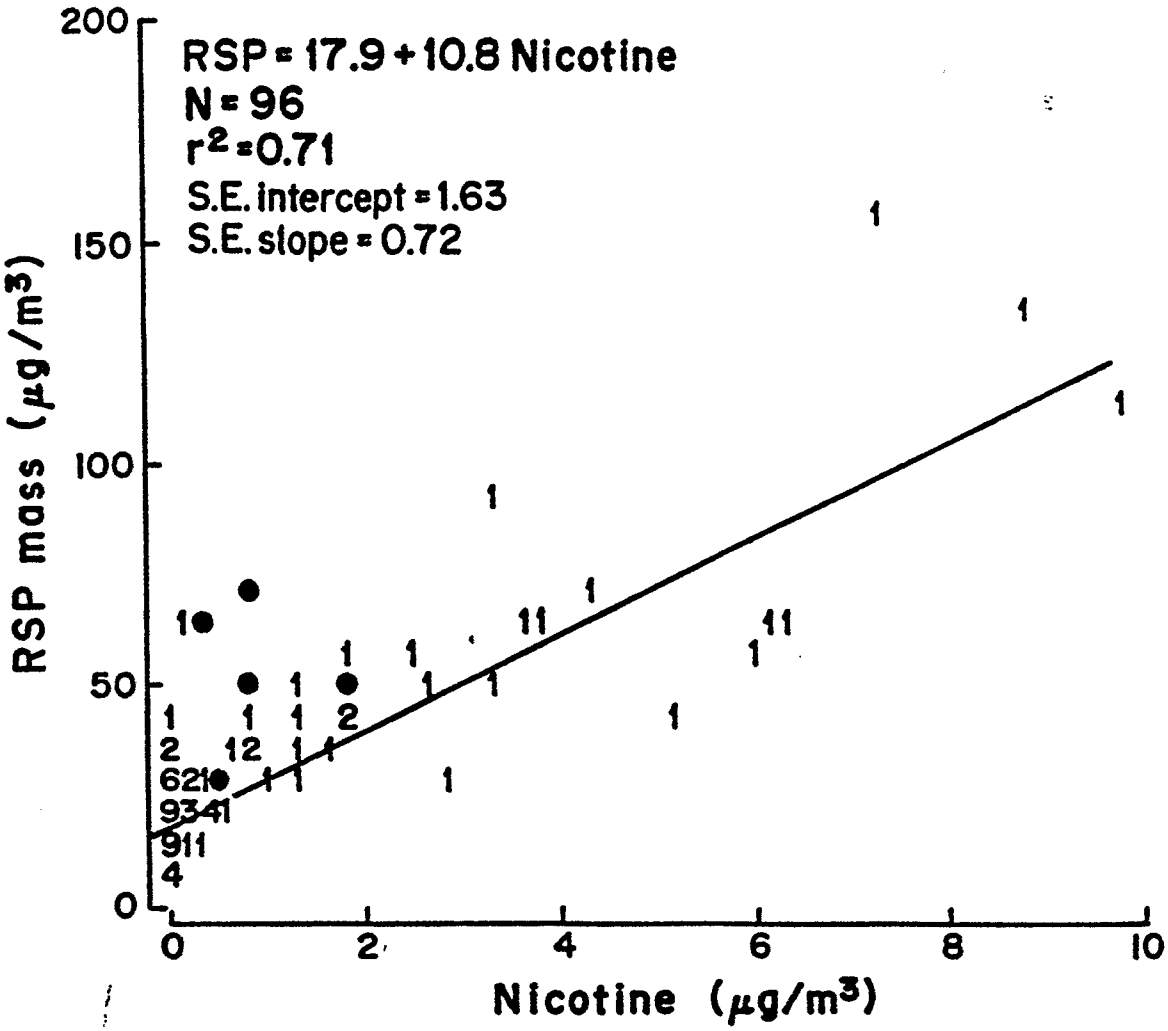

Figure 3-6. Week-long respirable suspended particle mass (RSP) and nicotine measurements in 96 residences with a mixture of sources. Numbers 1-9 refer to the number of observations at the same concentration.

Source: Leaderer and Hammond, 1991.

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levels associated with smoking occupancy (Figure 3-8) were calculated by subtracting particle levels for nonsmoking occupancy (presented in the studies) from the smoking occupancy levels. Thus, the increase in particle mass concentrations associated with ETS is presented in Figure 3-8. Indoor RSP levels in residences without smokers are typically in the range of 10-25 $\mu g/m^3$, while background office levels are somewhat lower (Figure 3-5).

The summary nicotine data (Figure 3-7) suggest that average nicotine values in residences with smoking occupancy will range from 2 to approximately 10 $\mu g/m^3$, with high values up to 14 $\mu g/m^3$ and low values down to 0.1 $\mu g/m^3$. Offices with smoking occupancy show a range of average nicotine concentrations similar to that of residences, but with considerably higher maximum values. The data from other indoor spaces suggest considerable variability, particularly in the range of maximum values. The cumulative distribution of weekly nicotine measured in one study (Leaderer and Hammond, 1991) for a sample of 96 homes, with the levels for smoking occupancy emphasized, is shown in Figure 3-9.

Particle mass concentrations in smoker-occupied residences show average increases of from 18 to 95 $\mu g/m^3$, while the individual increases can be as high as 560 $\mu g/m^3$ or as low as 5 $\mu g/m^3$ (Figure 3-8). Figure 3-10 (Leaderer and Hammond, 1991) highlights the distribution of weekly RSP concentrations for residences with smoking occupancy. In that study, smoking residences had RSP concentrations approximately 29 $\mu g/m^3$ higher than nonsmoking homes. Concentrations in offices with smoking occupancy will be on average about the same as those in residences. Interestingly, in a large and possibly the most comprehensive study of particle mass concentrations associated with smoking and nonsmoking sites in office buildings (Turk et al., 1987), the geometric mean concentration for RSP in 32 smoking sites was 44 $\mu g/m^3$ while the geometric mean for 35 nonsmoking sites was 15 $\mu g/m^3$. The difference of 29 $\mu g/m^3$ is the same as that found for smoking and nonsmoking residences (Figure 3-10). Restaurants, transportation, and other indoor spaces with smoking occupancy will result in a considerably wider range of average, minimum, and maximum increases in particle concentrations than the residential or office environments.

As noted earlier, indoor air contaminant concentrations are the result of the interaction of a number of factors related to the generation, dispersal, and elimination of the contaminants. Source use is no doubt the most important factor. Few studies have measured contaminant concentrations as a function of the smoking rate in residences or offices, but some data are available. One study estimated an average weekly contribution to residential RSP of 2-5 $\mu g/m^3$ per cigarette ([redacted], while another study estimated that a pack-a-day smoker would add 20 $\mu g/m^3$ to residential levels [redacted] estimated

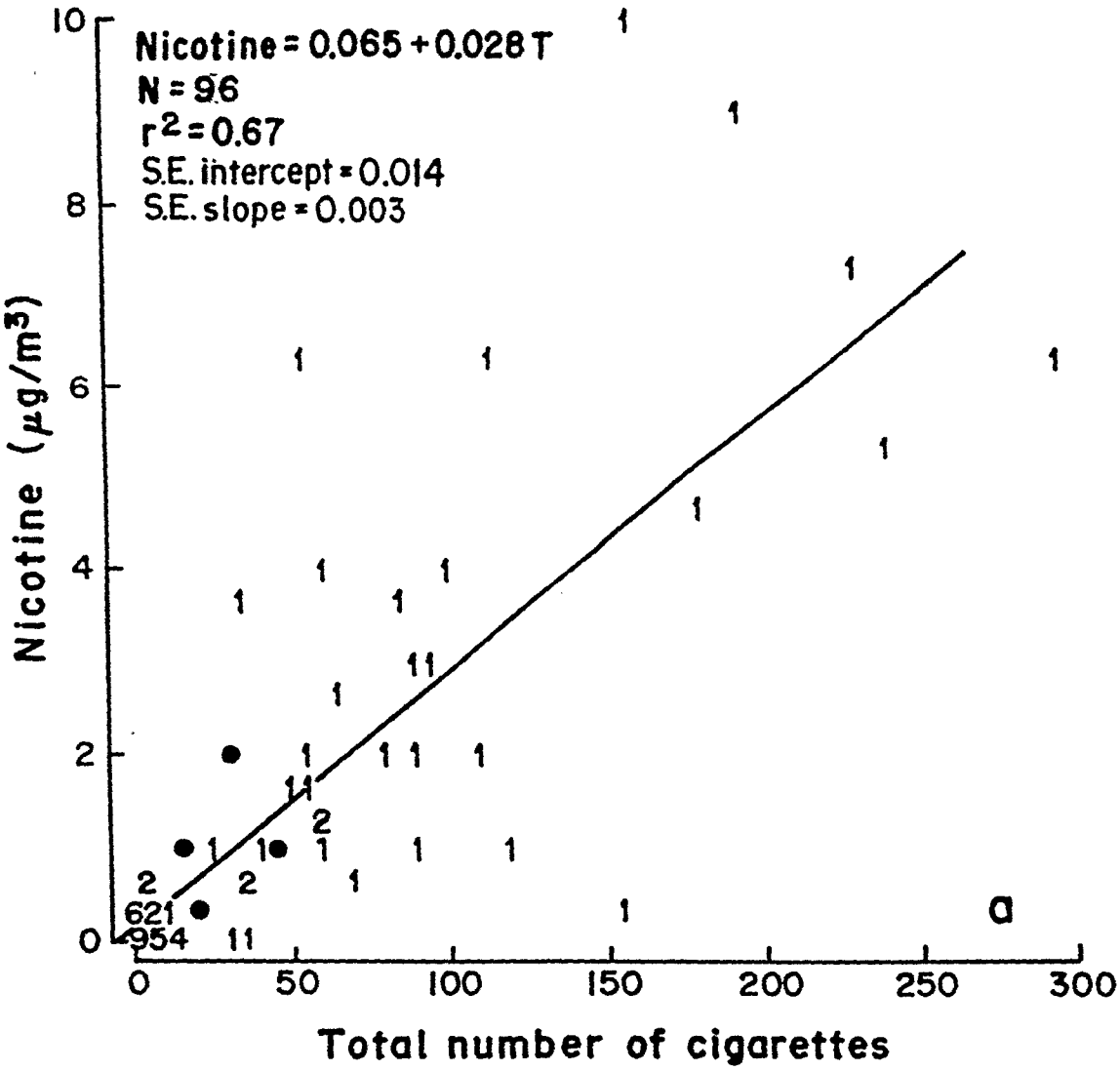

Figure 3-12a. Week-long nicotine concentrations measured in the main living area of 96 residences versus the number of questionnaire-reported cigarettes smoked during the air-sampling period. Numbers 1-9 refer to the number of observations at the same concentrations. Closed circles indicate that cigar or pipe smoking was reported in the houses, with each cigar or pipe smoked set equal to a cigarette. Data from residences in Onondaga and Suffolk Counties in New York State between January and April 1986. For panel (a), the standard errors for the intercept and slope are 0.014 and 0.002, respectively. For panel (b), the standard errors for the intercept and slope are 2.1 and 0.03, respectively.

Source: Leaderer and Hammond, 1991.

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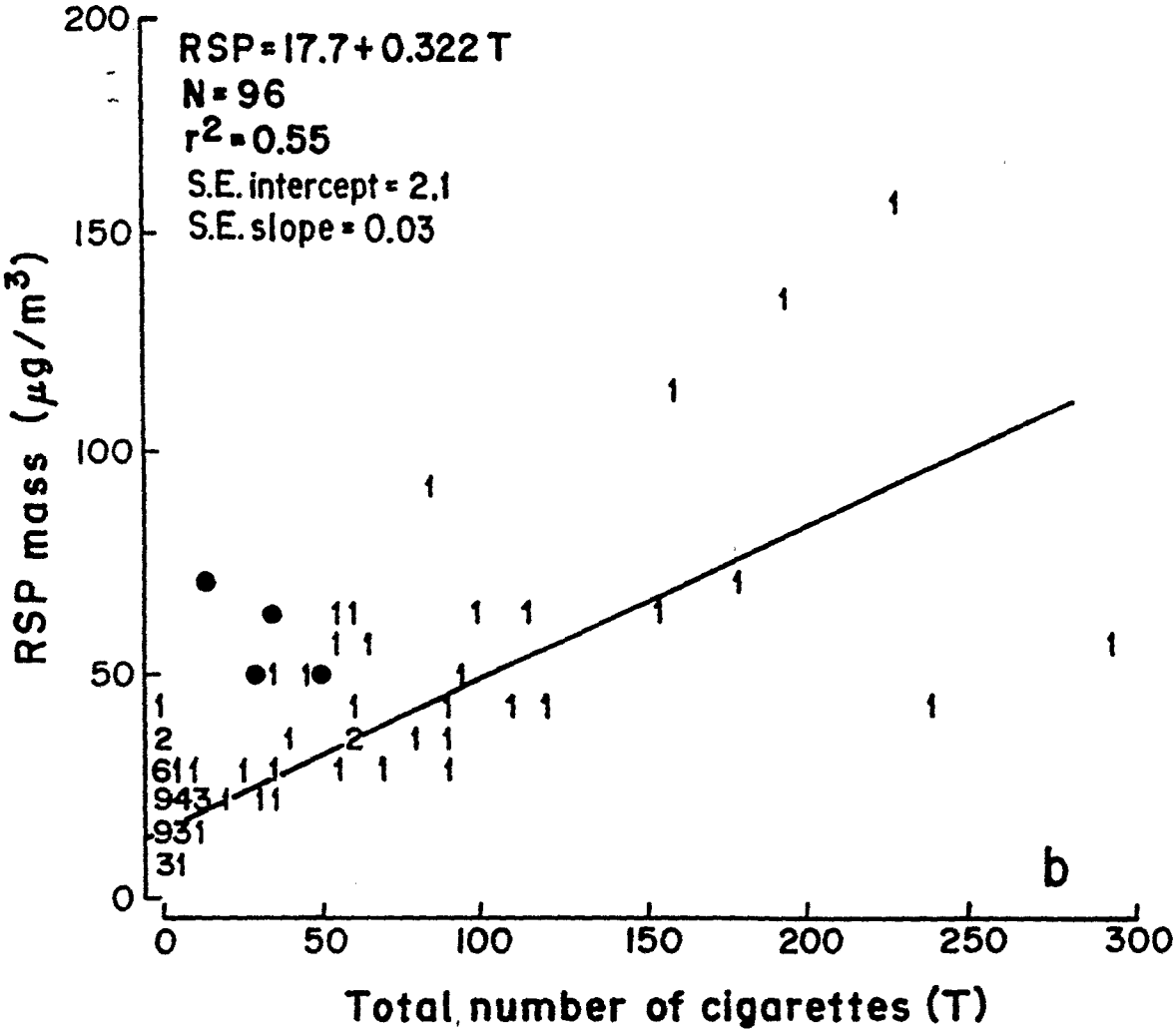

Figure 3-12b. Week-long respirable suspended particle mass (RSP) concentrations measured in the main living area of 96 residences versus the number of questionnaire-reported cigarettes smoked during the air-sampling period. Numbers 1-9 refer to the number of observations at the same concentrations. Closed circles indicate that cigar or pipe smoking was reported in the houses, with each cigar or pipe smoked set equal to a cigarette. Data from residences in Onondaga and Suffolk Counties in New York State between January and April 1986. For panel (a), the standard errors for the intercept and slope are 0.014 and 0.002, respectively. For panel (b), the standard errors for the intercept and slope are 2.1 and 0.03, respectively.

Source: Leaderer and Hammond, 1991.

in Table 3-4, indicate that activity and bedroom concentrations of nicotine in the children's homes increase with the number of cigarettes reported smoked in the home by parents. Concentrations also increased with the number of reported smokers in the household. Correlation coefficients over 0.7 were calculated between nicotine concentrations and number of cigarettes smoked. Exposure of children to ETS is covered in greater detail in Chapter 8.

It is important to note that while measurements of nicotine and ETS-associated RSP are good indicators of the contribution of ETS to air contaminant levels in indoor environments, their measurement does not directly constitute a measure of total exposure. The concentrations measured in all indoor environments have to be combined with time-activity patterns in order to determine average exposure of an individual as the sum of the concentrations in each environment weighted by the time spent in that environment. Both the home and the work environment (those without policies restricting smoking) have highly variable ETS concentrations, with the ranges largely overlapping. Which environment is most important in determining total exposure will vary with individual circumstances (e.g., a person who lives in a nonsmoking home but works in an office with smokers will receive most ETS exposure at work, but for those exposed both at home and at work, the home may be more important because, over the course of a week, more time is generally spent at home).

An additional issue to be considered is how well the general indoor concentrations represent exposures of individuals who may be directly exposed to the SS plume of ETS. Small children, particularly infants, held by smoking parents may receive exposures considerably higher than those predicted from concentrations reported for indoor spaces. Special consideration must be given to these significant subpopulations.

3.3.1.2.2. *Personal monitors.* Personal monitoring allows for a direct integrated measure of an individual's exposure. Personal air monitoring employs samplers (worn by individuals) that record the integrated concentration of a contaminant to which individuals are exposed in the course of their normal activity for time periods of several hours to several days. The monitors can be active (employing pumps to collect and concentrate the air contaminant) or passive (working on the principal of diffusion). As with biomarkers, personal monitoring provides an integrated measure of exposure to air contaminants across a number of environments where an individual spends time but does not provide direct information on concentrations of the air contaminant of interest in individual environments or on the level of exposure in each environment unless samples are taken in only one environment or are changed with each change of environment. Supplemental

Table 3-4. Weekly average concentrations of each measure of exposure by parental smoking status in the cross-sectional study, Minnesota, 1989

	Smoking status				
	Non-smokers	Light smokers	Father only	Mother only	Both parents
Number of subjects	23	4	8	6	7
Total cigarettes (no./week)	0.9	28.8	68.6	58.8	227.6
Activity room nicotine ($\mu g/m^3$)	0.15	0.32	2.45	5.50	12.11
Bedroom nicotine ($\mu g/m^3$)	-	0.30	1.21	2.66	5.32

information (air monitoring of spaces, time-activity patterns, etc.) is needed to determine the contribution of each microenvironment to total exposure.

Relatively few studies have measured personal exposures to ETS-associated nicotine and RSP for nonsmoking individuals. The few reported studies of personal exposure to nicotine are summarized in Table 3-5. Personal exposures associated with specific indoor environments are presented. Indoor environments include the nonindustrial workplace, homes, restaurants, public buildings, and transportation-related indoor spaces. Table 3-5 highlights the wide range of indoor environments in which ETS exposures take place and the wide range of personal exposures encountered in those environments. It is important to note, however, that relatively few observations are available and that observations for nonworkplace nicotine exposures are dominated by the Japanese data (Muramatsu), which may not be representative of personal exposures in the United States. Because the data are limited, specific conclusions about the contribution of different indoor environments to personal nicotine exposures associated with passive smoking cannot be drawn. The data do indicate, however, that a wide range of exposures to ETS takes place in a variety of indoor environments where smoking is permitted. The data also indicate that occupational and residential environments are important sources of exposure to ETS because of the levels encountered, which are comparable, and the amount of time individuals spend in them.

Studies of personal exposure to RSP of nonsmoking individuals that have attempted to stratify the collected data by ETS exposure are shown in Table 3-6. Three of the five studies represent exposures integrated over several different microenvironments (residential, public

Table 3-5. Studies measuring personal exposure to airborne nicotine associated with ETS for nonsmokers

Study	Setting	Subject	N	Nicotine, $\mu g/m^3$ X(±SD)	Nicotine, $\mu g/m^3$ Range	Comments
[redacted]	Airplane	Attendants	16	4.7 (±4.0)	0.1-10.5	4 attendants on 4 flights
[redacted]	Railroad	Clerks	40	6.9		Samples collected over work shifts
[redacted]	Workplace	Nonindustrial	15	20.4 (±20.6)		
[redacted]	Office	Volunteers	10	21.1		Calculated from data presented
	Laboratory		8	5.8		
	Conference room		5	38.7		
	Home		3	11.2		
	Hospital lobby		1	3.0		
	Hotel lobby		4	11.2		
	Restaurant		15	26.0		
	Transportation		22	21.7		
[redacted]	Office	Volunteers	3	6.9		Calculated from data presented
	Home		7	7.0		
	Restaurant		15	28.2		
	Car		7	40.0		
	Public transportation		1	11.4		

Table 3-6. Studies measuring personal exposure to particulate matter associated with ETS for nonsmokers

Study	Setting	Number of subjects			Particle mass, μg/m³		Particle mass due to ETS
		Total	No ETS exp.	ETS exp.	X (±SD)	Range	μg/m³
[redacted] et al.	24-hr. day	45			NR	NR	20[a]
[redacted]	24-hr. day	101			NR	NR	
			28		NR	NR	28[a]
				73	NR	NR	
[redacted] Sexton [redacted],	24-hr. day	48			NR	NR	
			NR		31.7	NR	18.4[1]
				NR	50.1	NR	
[redacted],	Workplace	15			63.9±41.5	4.0-145.8	
			1		4.0		64[2]
				14	68.2±39.5	14.7-145.8	
[redacted]	Workplace				86		3

[1]Calculated by authors from the regression line.
[2]Calculated from data presented, after the method of Leaderer and Hammond (1991).
[3]Calculated from nicotine exposure, after the method of Leaderer and Hammond (1991).

NR = not reported.

buildings, occupational, etc.), while two studies report exposures for the workplace only. Individuals reporting exposure to ETS have substantially higher integrated exposures to RSP than those reporting no exposure. Passive smoke exposure resulted in increases in personal RSP exposures of 18-64 $\mu g/m^3$. It is difficult to assess the ETS contribution to personal RSP levels for each indoor environment for the 24-hour RSP personal exposures. The contribution of each indoor environment must be substantially higher than the 24-hour averages presented, because exposures presumably did not occur during sleeping hours or in all microenvironments. Table 3-6 demonstrates that the contribution of ETS-related RSP in the work environment to personal exposure is important and variable.

The most extensive study of personal exposure to RSP clearly demonstrates the impact on RSP levels from ETS (Spengler et al., 1985). In this study, outdoor, indoor, and personal 24-hour concentrations of RSP (particle diameter ≤ 3.5 μm) were obtained for a sample of 101 nonsmoking individuals. Of the 101 nonsmokers, 28 persons reported some exposure to ETS in either the home or workplace, while 73 reported no ETS exposure. The cumulative frequency distributions of RSP for the ETS-exposed and non-ETS-exposed individuals and measured outdoor levels are shown in Figure 3-13. Those reporting ETS exposure had mean personal RSP levels 28 $\mu g/m^3$ higher than those reporting no ETS exposure (Table 3-6). A larger variation in RSP concentrations was also seen for those reporting ETS exposure.

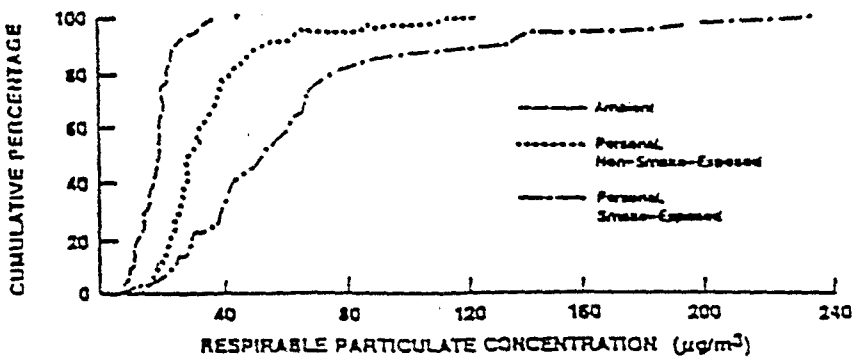

Figure 3-13. Cumulative frequency distribution of respirable suspended particle mass (RSP) concentrations from central site ambient and personal monitoring of smoke-exposed and nonsmoke-exposed individuals.

Source: [redacted]

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3.3.2. Biomarkers of ETS Exposure

Biomarkers of exposure are actually measures of dose or uptake and hence indicators that an exposure has taken place. Biomarkers, within the context of assessing exposure to air contaminants, refer to cellular, biochemical, or molecular measures obtained from biological media such as human tissues, cells, or fluids that are indicative of human exposure to air contaminants (NRC and Committee on Biological Markers, 1986; NRC, 1986; Hulka et al., 1990). The relationship between the biomarker and exposure, however, is complex and varies as a function of several factors, including environmental factors and the uptake, distribution, metabolism, and site and mode of action of the compound or compounds of interest.

Ideally, a biomarker of exposure for a specific air contaminant should be chemically specific, have a long half-life in the body, be detectable in trace quantities with high precision, be measurable in samples easily collected by noninvasive techniques, be inexpensive to assay, be either the agent associated with the effects or strongly associated with the agent of interest, and be quantitatively relatable to a prior exposure regimen. Ideal biomarkers for air contaminants, like markers for complex mixtures, do not exist.

Numerous biomarkers have been proposed as indicators for ETS (e.g., thiocyanate, carboxyhemoglobin, nicotine and cotinine, *N*-nitrosoproline, aromatic amines, protein or DNA adducts) (NRC, 1986; U.S. DHHS, 1986). While these biomarkers demonstrate that an exposure has taken place, they may not be directly related to the potential for developing the adverse effect under study (i.e., not the contaminant directly implicated in the effect of interest), they can show considerable variability from individual to individual, and they represent only fairly recent exposure (potentially inadequate for chronic outcomes). Furthermore, some of these markers may not be specific to ETS exposure (e.g., carboxyhemoglobin) while others (e.g., thiocyanate) may not be sensitive enough for ETS exposures.

Nicotine and its metabolite, cotinine, in the saliva, blood, and urine are widely used as biomarkers of active smoking and exposure to ETS and are valuable in determining total or integrated short-term dose to ETS across all environments (NRC, 1986; U.S. DHHS, 1986). Nicotine and cotinine are specific to tobacco and are accurately measured by gas chromatography, radioimmunoassay, or high pressure liquid chromatography in concentrations down to 1 ng/mL. Nicotine has a half-life of about 2 hours in the blood and is metabolized to cotinine and excreted in the urine. The short half-life of nicotine makes it a better indicator of very recent exposures than of integrated exposure.

Cotinine in saliva, blood, and urine is the most widely accepted biomarker for integrated exposure to active smoking or ETS (NRC, 1986; U.S. DHHS, 1986). Cotinine is the major

metabolite of nicotine, is specific to tobacco, and has a longer half-life for elimination from the body. The elimination half-life in smokers is approximately 20 hours (range of 10 to 37 hours), but it is typically longer in nonsmokers with ETS exposure, particularly in children (Figure 3-14) (Collier et al., 1990; Elliot and Rowe, 1975; Goldstein et al., 1987; Etzel et al., 1985; Greenberg et al., 1984). The half-life of cotinine makes it a good indicator of integrated ETS exposure over the previous day or two. Laboratory studies of nonsmokers exposed to acute high levels of ETS over varying times have shown significant uptake of nicotine by the nonsmokers and increases in their cotinine levels (NRC, 1986; U.S. DHHS, 1986; Hoffman et al., 1984; Russell and Feyerabend, 1975).

Cotinine, however, is not an ideal biomarker for ETS, and caution in its use has been suggested (Idle, 1990). Cotinine is only one of the metabolites of nicotine (trans-3'-hydroxycotinine has recently been identified as the major metabolite [Neurath et al., 1988]), and it shows considerable intersubject variability in controlled nicotine exposure studies (Idle, 1990). The assumption that nicotine is specific to tobacco has recently been questioned (Idle, 1990; Sheen, 1988; Castro and Monji, 1986; Davis et al., 1991). Plant sources other than tobacco, primarily from the Solanaceae family, which are common dietary components have been suggested as sources (e.g., eggplant, tomato, and green pepper). It has been suggested that nicotine in food is a natural defense against bacteria, fungi, insects, and animals (Ames, 1983).

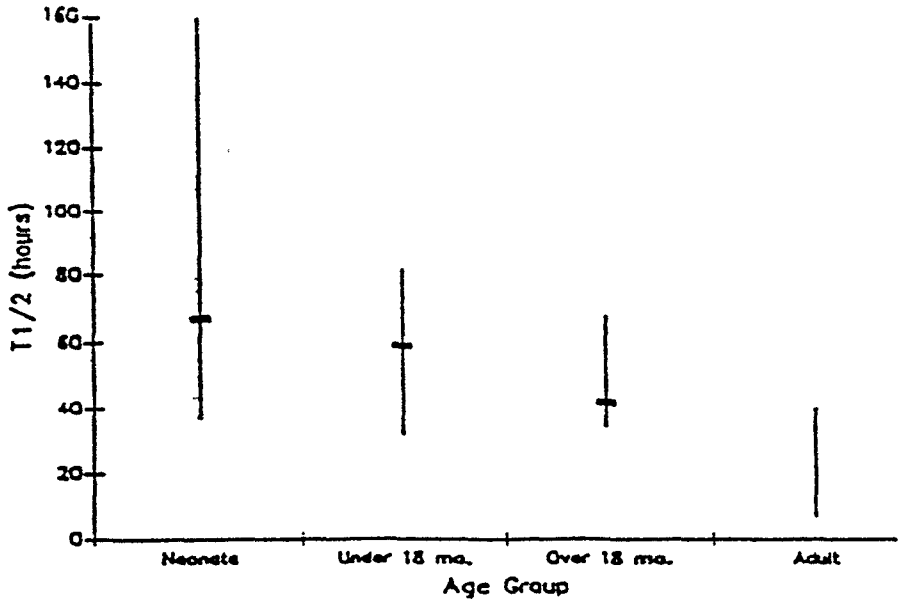

Figure 3-14. Average cotinine $t_{1/2}$ by age groups.

Source: Collier et al., 1990.

Tea has been identified as a particularly high source of dietary nicotine (Sheen, 1988). The impact of dietary nicotine, particularly tea, on cotinine levels of nonsmokers was evaluated in a study of 3,383 men and women 40-59 years of age as part of the Scottish Heart Health Study (Tunstall-Pedoe et al., 1991). The study found a small but inconsistent effect on serum cotinine levels with consumption of 10 or more cups of tea per day with no effect for consumption rates at fewer than 10 cups per day. The authors concluded that "cotinine levels in true nonsmokers reflect far more the nicotine in inhaled ambient tobacco smoke than they do nicotine in tea."

In the most detailed evaluation of nicotine in food, Davis et al. (1991) measured nicotine in a number of teas and foods. They found nicotine levels ranging from less than detectable to 285 ng/g wet weight. The authors calculated that with consuming average quantities of tomatoes, potatoes, cauliflower, and black tea, the average contribution to urinary cotinine levels would be 0.6 ng/mL. High consumption of the foods and tea might result in a maximum urinary cotinine level of 6.2 ng/mL. The average contribution of dietary nicotine intake to urinary cotinine levels might be expected to be below 1 ng/mL and somewhat higher under conditions of high consumption of nicotine-containing foods.

Several population-based studies examined cotinine levels in smokers, nonsmokers reporting passive smoke exposure, and nonsmokers reporting no passive smoke exposure (NRC, 1986; U.S. DHHS, 1986; Greenberg et al., 1984; Wald et al., 1984; Wald and Ritchie, 1984; Jarvis et al., 1985; Coultas et al., 1987; Riboli et al., 1990; Cummings et al., 1990; Tunstall-Pedoe et al., 1991). These studies found that exposure to ETS is highly prevalent even among those living with a nonsmoker (e.g., Cummings et al., 1990). Saliva, serum, and urine cotinine levels in ETS-exposed nonsmokers are generally higher than those in nonsmokers reporting no ETS exposure, and levels of cotinine are considerably higher in smokers than those in nonsmokers passively exposed (e.g., Table 3-7). Cotinine levels in nonsmokers exposed to ETS are approximately 1% of the levels in active smokers. Cotinine levels of nonsmokers have been found to increase with self-reported ETS exposure (e.g., Figures 3-15 and 3-16).

In a 10-country study of ETS exposure of 1,369 nonsmoking women (Riboli et al., 1990), average urinary levels of cotinine/creatinine by country ranged from approximately 2.5 ng/mg for Shanghai to approximately 14 ng/mg for Trieste. Eighty percent of those sampled had a detectable level of cotinine. Statistically significant differences were observed between centers with lowest values observed in Honolulu, Shanghai, and Chandigarh and the highest values in Trieste, Los Angeles, and Athens. This study also found an increase in cotinine/creatinine levels from the group of women reporting no ETS exposure either at home or work (lowest exposure) to the group reporting ETS exposure both at home and at work, the highest exposure group

Table 3-7. Approximate relations of nicotine as the parameter between nonsmokers, passive smokers, and active smokers

Nicotine/cotinine	Nonsmokers without ETS exposure (N = 46)		Nonsmokers with ETS exposure (N = 54)		Active smokers (N = 94)
	Mean value	% of active smokers' value	Mean value	% of active smokers' value	Mean value
Nicotine (ng/mL):					
in plasma	1.0	7.0	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1[1]	0.7	1,750
Cotinine (ng/mL):					
in plasma	0.8	0.3	2.0[1]	0.7	275
in saliva	0.7	0.2	2.5[2]	0.8	310
in urine	1.6	0.1	7.7[2]	0.6	1,390

[1]Differences between nonsmokers exposed to ETS compared with nonsmokers without exposure: $p < 0.01$.
[2]Differences between nonsmokers exposed to ETS compared with nonsmokers without exposure: $p < 0.001$.

Source: Jarvis, 1987.

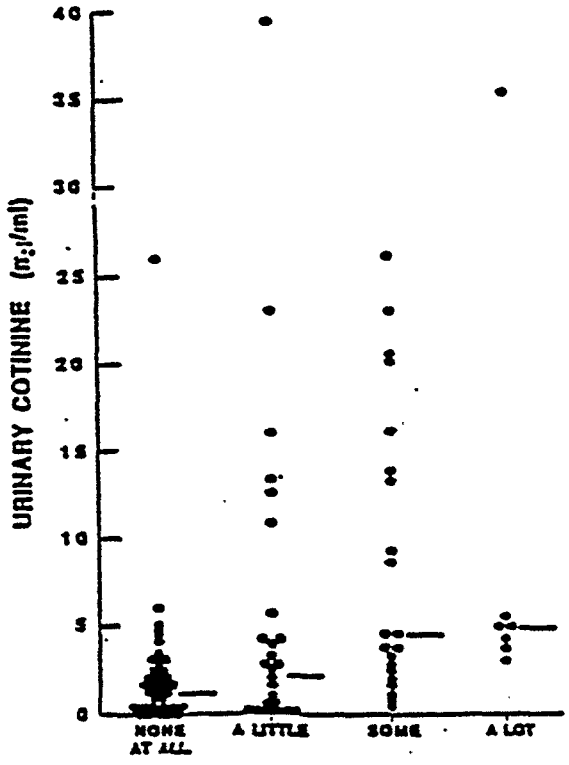

Figure 3-15. Distribution of individual concentrations of urinary cotinine by degree of self-reported exposure to ETS. Horizontal bars indicate median values.

Source: Jarvis and Russell, 1985.

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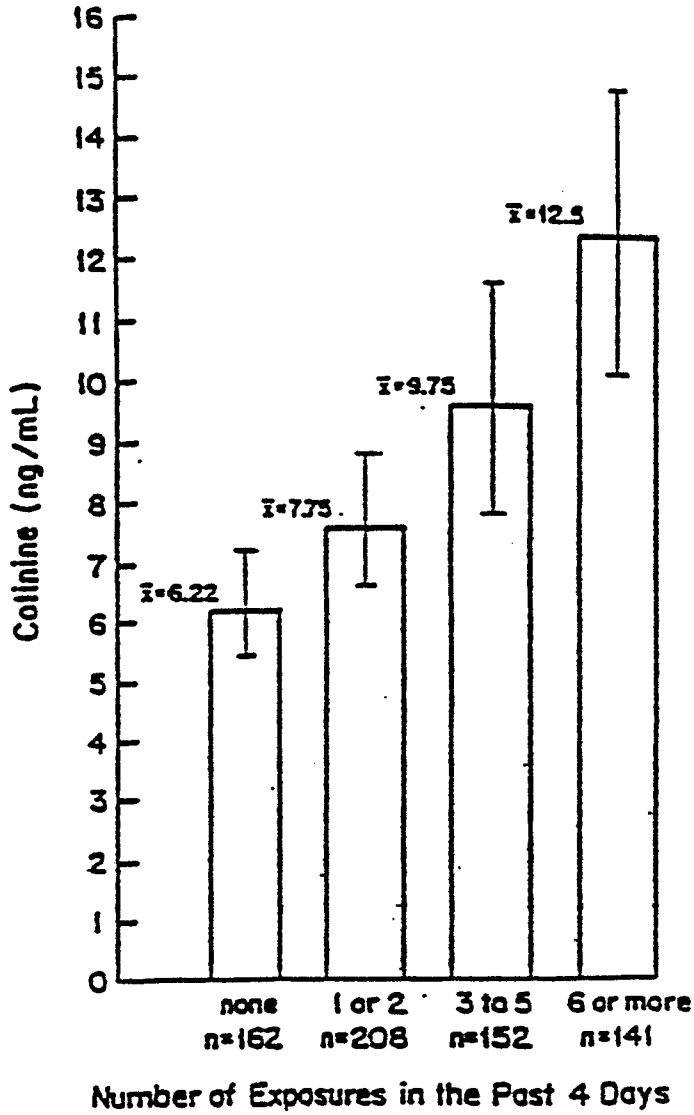

Figure 3-16. Urinary cotinine concentrations by number of reported exposures to tobacco smoke in the past 4 days among 663 nonsmokers, Buffalo, New York, 1986.

Source: Cummings et al., 1990.

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(Figure 3-17). The group of women reporting ETS exposure only at home had cotinine/creatinine levels approximately 60% of those who reported exposure both at home and at work.

Urinary cotinine levels also were found to increase with the number of questionnaire-reported ETS exposures in a group of 663 never-smokers and ex-smokers (Cummings et al., 1990). In that study, 76% of the subjects reported passive smoke exposure in the 4-day period preceding the sampling. Of the total sample, 91% had detectable cotinine levels. Among the 76% reporting ETS exposure, 28% reported exposure at work, 27% at home, 16% in restaurants, 11% at social gatherings, 10% in a car or airplane, and 8% in public buildings. Cotinine levels in this study were also found to vary by month, with the winter months being associated with higher levels and corresponding to higher reported exposures.

Cotinine values in smokers and nonsmokers measured in both the laboratory or field setting show considerable variability due to individual differences in the uptake, distribution, metabolism, and elimination of nicotine. Another issue to be considered in interpreting the field data is that exposure status is determined by respondent self-reporting. This can lead to a misclassification error, which tends to reduce the differences in cotinine levels measured in the ETS-exposed versus non-ETS-exposed groups and to increase the variability in the levels within any exposure category. Within the exposed group, this misclassification error could either increase or decrease the average cotinine levels measured.

It is important to recognize that nicotine and cotinine are actually proxy biomarkers. They may not be the active agents in eliciting the adverse effect under study but merely indicative of the level of passive smoke exposure. Using these measures to estimate cigarette equivalents or determine equivalent active smoking exposure could result in over- or underestimating exposure to individual or classes of compounds that may be more directly related to the health or nuisance effect of concern. Use of different biomarker proxies (e.g., protein adducts) could result in estimates of much larger cigarette equivalent doses.

Nevertheless, nicotine and cotinine levels in ETS-exposed nonsmokers measured in laboratory and field studies have been used to estimate cigarette equivalent exposures and to equate ETS exposures with active smoker exposures (NRC, 1986; U.S. DHHS, 1986; Jarvis, 1989). On an equivalent cigarette basis, an upper-bound estimate of nicotine dose of 2.5 mg/day for a passive smoke exposure has been proposed (Jarvis, 1989). This would translate into the equivalent of about one-fifth of a cigarette per day or about 0.7% of the average smoker's dose of nicotine (cigarette equivalent dose of other toxins or carcinogens would be different--see above). Comparisons of cotinine values in ETS-exposed nonsmokers with those measured in smokers ranged from 0.1% to 2%. One analysis proposed that, on average, nonsmokers' cotinine levels are 0.5%-0.7% of those found in cigarette smokers (Jarvis, 1989). It should be noted that these

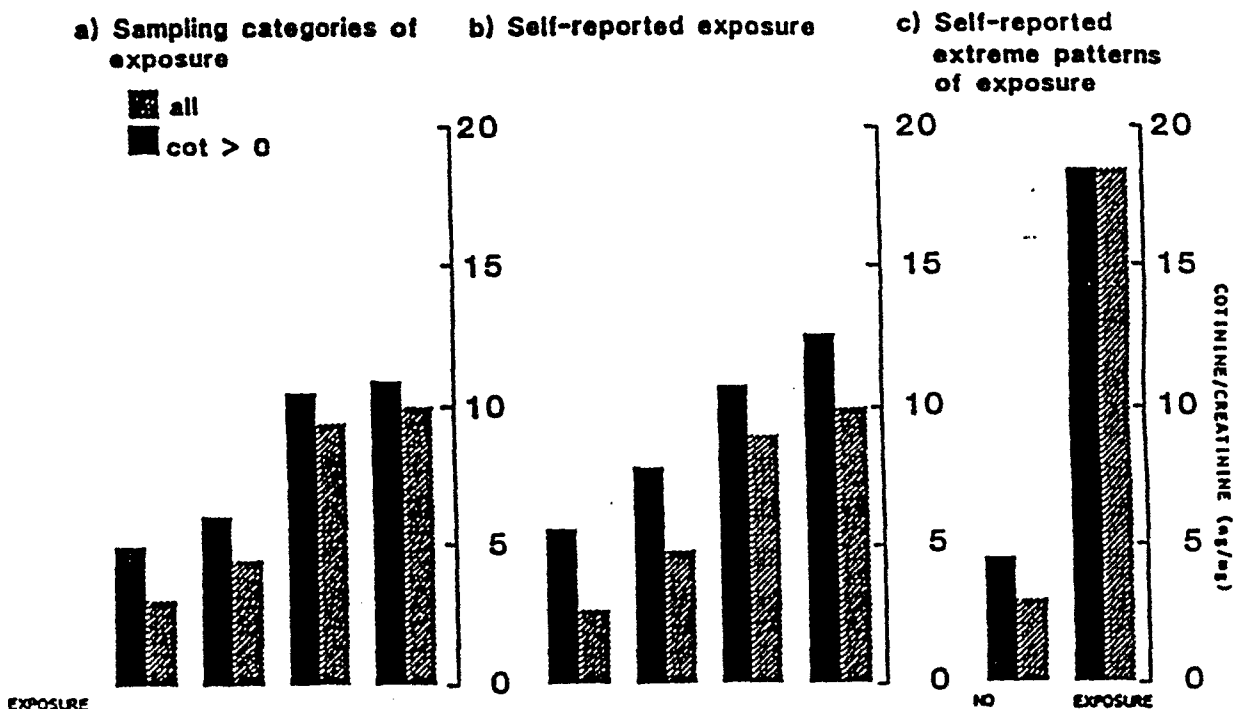

Figure 3-17. Average cotinine/creatinine levels for subgroups of nonsmoking women defined by sampling categories of exposure or by self-reporting exposure to ETS from different sources during the 4 days preceding collection of the urine sample.

Source: Riboli et al., 1990.

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estimations are based on a number of assumptions that may not hold (e.g., the half-life of nicotine and cotinine in smokers and nonsmokers being the same).

One of the protein adducts used as a biomarker of active and passive smoking is the 4-aminobiphenyl adduct of hemoglobin. One advantage of hemoglobin adducts is that their half-life is quite long and they will persist through the life of a red blood cell, which is approximately 120 days. Therefore, levels of 4-ABP-Hb adducts reflect exposures over the past several weeks, rather than the day or two of exposure integration reflected by cotinine measurements.

Tobacco smoke is the primary environmental source of 4-aminobiphenyl (its use in the dye industry was discontinued decades ago), and smokers have between 5 and 8 times as much 4-ABP-Hb adducts as nonsmokers (Hammond et al., 1990; Perera et al., 1987; Maclure et al., 1989). That nonsmokers appear to have approximately 10-20% the adduct level as smokers may at first appear to be contradictory to the urinary cotinine ratios of about 1%, but in fact both results are quite consistent with our knowledge of the emissions of various contaminants in mainstream and sidestream smoke. Approximately twice as much nicotine is emitted in sidestream as in mainstream smoke, but about 31 times as much 4-ABP is emitted in SS as in MS. Thus, compared to MS, SS is 15 times more enriched in 4-ABP than in nicotine. Similarly, the ratio of biomarkers in those exposed to ETS compared with smokers is roughly 15 times greater for the biomarker 4-ABP-Hb adducts than for the biomarker cotinine, a metabolite of nicotine.

The above discussions indicate that the cigarette equivalent dose of those exposed to ETS varies with the compound, so that a passive smoker may receive 1% as much nicotine as an active smoker but 15% as much 4-ABP. These examples demonstrate the importance of careful interpretation of biomarkers in estimating doses.

3.3.3. Questionnaires for Assessing ETS Exposures

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective and prospective studies of acute and chronic effects. They are the least expensive method to obtain ETS exposure information for large populations. They can be used to provide a simple categorization of ETS exposure, to determine time-activity patterns of individuals (e.g., how much time is spent in environments where smoking occurs), and to acquire information on the factors or properties of the environment affecting ETS concentrations (e.g., number of cigarettes smoked, size of indoor environments, subjective evaluation of level of smokiness). The time-activity pattern information is combined with measured or estimated concentrations of ETS in each environment to provide an estimate of total exposure. Information on the factors affecting ETS concentrations is used to model or predict ETS levels in those environments.

Questionnaires are used most extensively to provide a simple categorization of potential ETS exposure (e.g., do you live with a smoker?, are you exposed to ETS at your place of work?, how many hours a week are you exposed to ETS?) and to obtain information on possible confounders (e.g., occupational history, socioeconomic status). When used simply to determine a dichotomous exposure (ETS-exposed vs. unexposed), any misclassification tends to bias measures of association toward the null. Thus, any effect that may be present will be underestimated or even may not be detectable. If there are more than two exposure categories (e.g, light, medium, or heavy exposure), the intermediate categories of exposure may be biased either away from or toward the null. Misclassification errors may arise from respondents' (1) lack of knowledge, (2) biased recall, (3) memory failure, and (4) intentional alteration of information. Additionally, there are investigator-based sources of misclassification. Errors may arise if semiquantitative levels are incorrectly imputed to answers; e.g., even if house exposures are higher than occupational exposures on average, for any given individual the ranking may well be reversed from that of the average.

In using questionnaires to assess exposure categories to ETS, to determine time-activity patterns, and to acquire information on the factors affecting concentrations, it is important to minimize the uncertainty associated with the estimate and to characterize the direction and magnitude of the error.

Unlike for active smoking assessment, standardized questionnaires for assessing ETS exposures in prospective or retrospective studies of acute or chronic health or nuisance effects do not exist. Lebowitz et al. (1989) reported on an effort to develop a standardized questionnaire to assess ETS exposure in various indoor environments. This questionnaire, however, has not yet been validated. Questionnaires used to assess ETS exposure typically have been developed for specific studies and have not been validated for general use. There is no "gold standard" with which to validate the questionnaires. Various strategies, however, have been used to assess the validity of diverse types of questionnaires used to assess ETS exposure. Efforts to validate questionnaires have used survey data, air monitoring of nicotine in various microenvironments, and nicotine or cotinine in body fluid samples.

A recent study (Leaderer and Hammond, 1991) of 96 homes using a questionnaire to assess residential smoking and a passive nicotine air monitor found that 13% of the residences reporting no smoking had measurable levels of nicotine while 28% of the residences reporting smoking had nondetectable levels of nicotine. A good level of agreement between questionnaire-reported number of cigarettes smoked and residential levels of ETS-related RSP and nicotine was observed in this study (Figures 3-12a and 3-12b).

Studies (Marbury et al., 1990; Coghlin et al., 1989; Coultas et al., 1987, 1990a, 1990b; Riboli et al., 1990; Cummings et al., 1990) comparing various measures of ETS exposure (location of exposure, intensity of exposure, duration of exposure, number of cigarettes smoked, etc.) with cotinine levels measured in physiological fluids generally meet with only moderate success (explained variations on the order of 40% or less). The largest such study (Riboli et al., 1990) was a collaborative effort conducted in 10 countries; correlations in the range of 0.3 to 0.51 ($p < 0.01$) were found between urinary cotinine levels and various measures of exposure derived from questionnaire data. Using cotinine as a biomarker of exposure, studies indicated that a substantial percentage of those reporting no ETS exposure by questionnaire do have measurable exposure. Differences in the uptake, metabolism, and excretion of nicotine among individuals make it difficult to use this measure as a "gold standard" in validating questionnaires. Also, the recent exposure (previous 1-2 days) that is measured by cotinine may differ from usual exposure.

In a study involving 10 homes with 20 nonsmoking and 11 homes with smoking residents, the variability of four markers of ETS exposure (questionnaires, cotinine in saliva and urine, respirable suspended particle mass in air, and nicotine in air) was assessed (Coultas et al., 1990b). Questionnaire-reported exposures explained less than 10% of the variability in air concentrations of suspended particle mass and nicotine, 8% of the variability in urinary cotinine, and 23% of the variability in saliva cotinine. The authors concluded that multiple exposure assessment measurement tools were needed to assess ETS exposure in the home.

In one effort to develop a validated questionnaire (Coghlin et al., 1989), 53 subjects were asked detailed questions about their exposures to ETS, including location of exposures, number of smokers, ventilation characteristics, number of hours exposed, proximity of smokers, and intensity of ETS. They then wore a passive sampler for nicotine for 7 days and recorded the same information regarding each exposure episode in daily diaries. Formulae were developed to score the exposures on both the questionnaire and the diary, and these scores were then correlated to the average nicotine concentrations measured over the 7-day period. Excellent correlation was found ($r^2 = 0.83$ for the questionnaire and 0.90 for the diary). However, the simple questions that have been used most frequently in epidemiologic studies, such as whether a subject lived with a smoker or the number of hours the subject was exposed, were not nearly as well correlated with the measured exposures. These results indicate that reliable questionnaires can be developed, but that those used in most studies in the past will lead to some random misclassification of exposure, and, hence, underestimation of any effect that may be present.

More recently, epidemiologic studies of acute and chronic respiratory effects in children associated with ETS exposure have utilized questionnaires in combination with measurements of cotinine levels in physiologic fluids (Ehrlich et al., 1992; Reese et al., 1992; Etzel et al., 1992).

The studies provide more of a direct link between questionnaire-assessed exposures and objective measures of exposure and disease. Such studies, discussed in Chapter 8, not only provide a means of validating questionnaires but also provide data to establish validation of the risk models used in Chapter 8.

ETS exposures take place across a number of environments, with an individual's total exposure being a function of the amount of time spent in each environment and the concentration in that environment. Questionnaires need to assess exposures across indoor environments. Personal air monitoring provides a method to validate ETS exposure assessment questionnaires and to assess the contribution of each environment to total current exposure.

Personal air monitoring and cotinine measurements in combination with questionnaires have highlighted the importance of obtaining information on spouses' smoking status, smoking at home, smoking at work, smoking in various other indoor environments (social settings, vehicles, public places, etc.), amount of time in environments where smoking occurs, and the intensity of the exposure (Marbury et al., 1990; Coghlin et al., 1989; Coultas et al., 1987, 1990a, 1990b; Riboli et al., 1990; Cummings et al., 1990).

3.4. SUMMARY

ETS is a major source of indoor air contaminants. The ubiquitous nature of ETS in indoor environments indicates that some unintentional inhalation of ETS by nonsmokers is virtually unavoidable. ETS is a dynamic complex mixture of over 4,000 chemicals found in both vapor and particle phases. Efforts to characterize the physical and chemical properties of SS emissions, the principal component of ETS, have found that: (1) MS and SS emissions are qualitatively very similar in their chemical composition, containing many of the same carcinogenic and toxic compounds, (2) several of these compounds, including five known human carcinogens, nine probable human carcinogens, three animal carcinogens, and several toxic agents, are emitted at higher levels in SS than MS smoke (sometimes by an order of magnitude or more); (3) SS emissions of these notable air contaminants demonstrate little variability among brands of cigarettes. The enrichment of several known or suspected carcinogens in SS relative to MS smoke suggests that the SS contaminant mix may be even more carcinogenic than the MS mix, per unit of tobacco burned.

Sidestream emissions, while enriched in several notable air contaminants, are quickly diluted into the environment where ETS exposures take place. Air sampling conducted in a variety of indoor environments has shown that nonsmoker exposure to ETS-related toxic and carcinogenic substances will occur in indoor spaces where there is smoking occupancy. Individuals close to smokers (e.g., an infant in a smoking parent's arms) may be directly exposed

to the plume of SS or exhaled MS, and thus be more heavily exposed than indoor measurements from stationary air monitors might indicate.

Given the complex nature of ETS, it is necessary to identify marker or proxy compounds that when measured will allow for the quantification of exposure to ETS. Vapor phase nicotine and respirable suspended particle mass are two such markers that are suitable indicators of exposure to ETS. Nicotine and RSP have been measured in personal monitoring studies and in studies of a variety of indoor environments. The results of these studies clearly demonstrate that reported exposure to ETS, even under the conditions of low frequency, duration, and magnitude, will result in RSP and nicotine values above background. These studies indicate that ETS exposures take place in a wide range of environments (residences, workplaces, restaurants, airplanes, etc.,) where smoking occurs. Indoor levels of RSP and vapor phase nicotine have been shown to vary in a linear fashion with reported tobacco consumption. Nicotine levels measured indoors have ranged from less than 1 $\mu g/m^3$ to over 500 $\mu g/m^3$, while RSP levels have ranged from less than 5 $\mu g/m^3$ to over 1 mg/m^3. Nicotine exposures greater than 100 $\mu g/m^3$ are exceedingly rare; most environments measured have ranged from less than 0.3 (smoke free) to 30 $\mu g/m^3$; bars and smoking sections of planes may reach 50-75 $\mu g/m^3$. Thus, the normal range of ETS exposures is approximately 100-fold: 0.3 to 30 $\mu g/m^3$ for nicotine and from 5 to 500 $\mu g/m^3$ for RSP.

In residences with smoking occupancy, average daily or weekly nicotine values might typically range from less than 1 to 10 $\mu g/m^3$, varying principally as a function of number of smokers or number of cigarettes smoked. Average daily or weekly residential concentrations of ETS-associated RSP could be expected to increase from 18 to 95 $\mu g/m^3$ (added to background levels) in homes where smoking occurs. Like nicotine, ETS-associated RSP increases with increased smoking. Average levels of nicotine and RSP in offices with smoking occupancy are roughly comparable to those in homes.

Cotinine in saliva, blood, and urine, while not an ideal biomarker, is the most widely accepted biomarker of ETS exposure. Cotinine is an excellent indicator that ETS exposure has taken place. It also establishes the link between exposure and uptake. Studies show that cotinine levels correlate with levels of ETS exposure. The available data also indicate that as many as 80% of nonsmokers are exposed to ETS and that there is variability in average exposure levels among nonsmokers in different geographical regions.

Although average cotinine levels are a useful indicator of relative doses of ETS among different groups of nonsmokers, the ratio of cotinine levels in nonsmokers versus smokers may not be indicative of the exposure ratio for the active agents in ETS and MS responsible for the adverse effects. For example, while comparisons of cotinine levels in smokers and nonsmokers have led to

estimates that ETS-exposed nonsmokers receive from 0.1 to 0.7% of the dose of nicotine of an average smoker, ETS-exposed nonsmokers may receive 10-20% of the dose of 4-ABP that smokers inhale.

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective and prospective studies of acute and chronic effects. They have been used not only to establish simple categories of ETS exposure but also to obtain information on activity patterns of exposed individuals and on environmental factors affecting concentrations in different indoor environments. No standardized or validated questionnaires have yet been developed for assessing ETS exposure. A number of studies have compared questionnaire responses to measured air concentrations of nicotine and RSP and to cotinine levels. These efforts have indicated that a significant percentage of individuals reporting no exposure had actually been exposed. In general, questionnaires had moderate success in assessing exposure status and level of exposure. Misclassification errors must be addressed when using questionnaires to assess ETS exposure.

In summary, ETS represents an important source of toxic and carcinogenic indoor air contaminants. The available data suggest that exposure to ETS is widespread, with a wide range of exposure levels.

4. HAZARD IDENTIFICATION I: LUNG CANCER IN ACTIVE SMOKERS, LONG-TERM ANIMAL BIOASSAYS, AND GENOTOXICITY STUDIES

4.1. INTRODUCTION

Numerous epidemiologic studies have conclusively established that the tobacco smoke inhaled from active smoking is a human lung carcinogen (U.S. DHHS, 1982; IARC, 1986). A clear dose-response relationship exists between lung cancer and amount of exposure, without any evidence of a threshold level. It is, therefore, reasonable to theorize that exposure to environmental tobacco smoke (ETS) might also increase the risk of lung cancer in both smokers and nonsmokers.

As documented in the previous chapter, the chemical compositions of mainstream smoke (MS) and ETS are qualitatively similar, and both contain numerous known or suspected human carcinogens. In fact, ETS contains essentially all of the same carcinogens identified in MS, and many of these appear in greater amounts in sidestream smoke (SS), the primary component of ETS, than in MS, per unit tobacco burned (Table 3-1). In addition, both MS and SS have been shown to be carcinogenic in animal bioassays (Wynder and Hoffman, 1967; Grimmer et al., 1988), and MS, SS, and ETS have all been found to be genotoxic in in vitro systems (IARC, 1986). Furthermore, as the previous chapter also describes, exposure assessments of indoor air and measurements of nicotine and cotinine levels in nonsmokers confirm that passive smokers are exposed to and absorb appreciable amounts of ETS that might result in elevated lung cancer risk.

This chapter reviews the major evidence for the lung carcinogenicity of tobacco smoke derived from human studies of active smoking and the key supporting evidence from animal bioassays and in vitro experiments. The evidence from the few animal and mutagenicity studies pertaining specifically to ETS is also presented. The majority of this information has already been well documented by the U.S. Department of Health and Human Services (U.S. DHHS) (1982) and the International Agency for Research on Cancer (IARC) (1986). The current discussion mainly extracts and summarizes some of the important issues and principal studies described in those comprehensive reports.

In view of the abundant and consistent human evidence establishing the carcinogenic potential of active smoking to the lung, the bulk of this chapter focuses on the human data. Although EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a) suggest an extensive review of all evidence pertaining to carcinogenicity, we believe that the large quantity of human cancer studies on both MS and ETS provide the most appropriate database from which to evaluate the lung cancer potential of ETS. Thus, the animal evidence and genotoxicity results are given only limited attention here. Similarly, a discussion of the mutagenicity data for individual smoke

components would be superfluous in the context of the overwhelming evidence from other, more pertinent sources and is not included. Extensive reviews of these data can be found in the U.S. DHHS (1982) and IARC (1986) publications. Claxton et al. (1989) provide an assessment of the genotoxicity of various ETS constituents.

4.2. LUNG CANCER IN ACTIVE SMOKERS

Studies of active smoking in human populations from many countries provide direct and incontrovertible evidence for a dose-related, causal association between cigarette smoking and lung cancer. This evidence includes time trends in lung cancer mortality rates associated with increasing cigarette consumption, high relative risks for lung cancer mortality in smokers of both sexes observed consistently in numerous independent retrospective and prospective studies, and dose-response relationships demonstrated with respect to smoking intensity and duration and for all four major histological types of lung cancer.

4.2.1. Time Trends

While the overall cancer death rate in the United States has been fairly stable since 1950, the lung cancer death rate has increased drastically for both males and females (Figures 4-1 and 4-2). Age-adjusted lung cancer mortality rates in men have increased from 11 per 100,000 in 1940 to 73 per 100,000 in 1982, leveling slightly to 74 per 100,000 in 1987 (Garfinkel and Silverberg, 1991). In women, lung cancer mortality rates have risen from 6 per 100,000 in the early 1960's to 28 per 100,000 in 1987 (Garfinkel and Silverberg, 1991).

The striking time trends and sex differences seen in lung cancer mortality rates correlate with historical smoking patterns. Increases in lung cancer death rates parallel increases in cigarette consumption with a roughly 20-year lag time, accounting for the latency period for the development of smoking-induced lung cancer. Males started smoking cigarettes in large numbers during the years around World War I, whereas females did not begin smoking in appreciable numbers until World War II. Cigarette consumption per capita (based on the total population age 18 and older) in the United States rose from 1,085 in 1925 to a high of 4,148 in 1973. In the past two decades, cigarette consumption has decreased to 2,888 in 1989 (Garfinkel and Silverberg, 1991). This decline correlates with the leveling off of lung cancer mortality rates in recent years.

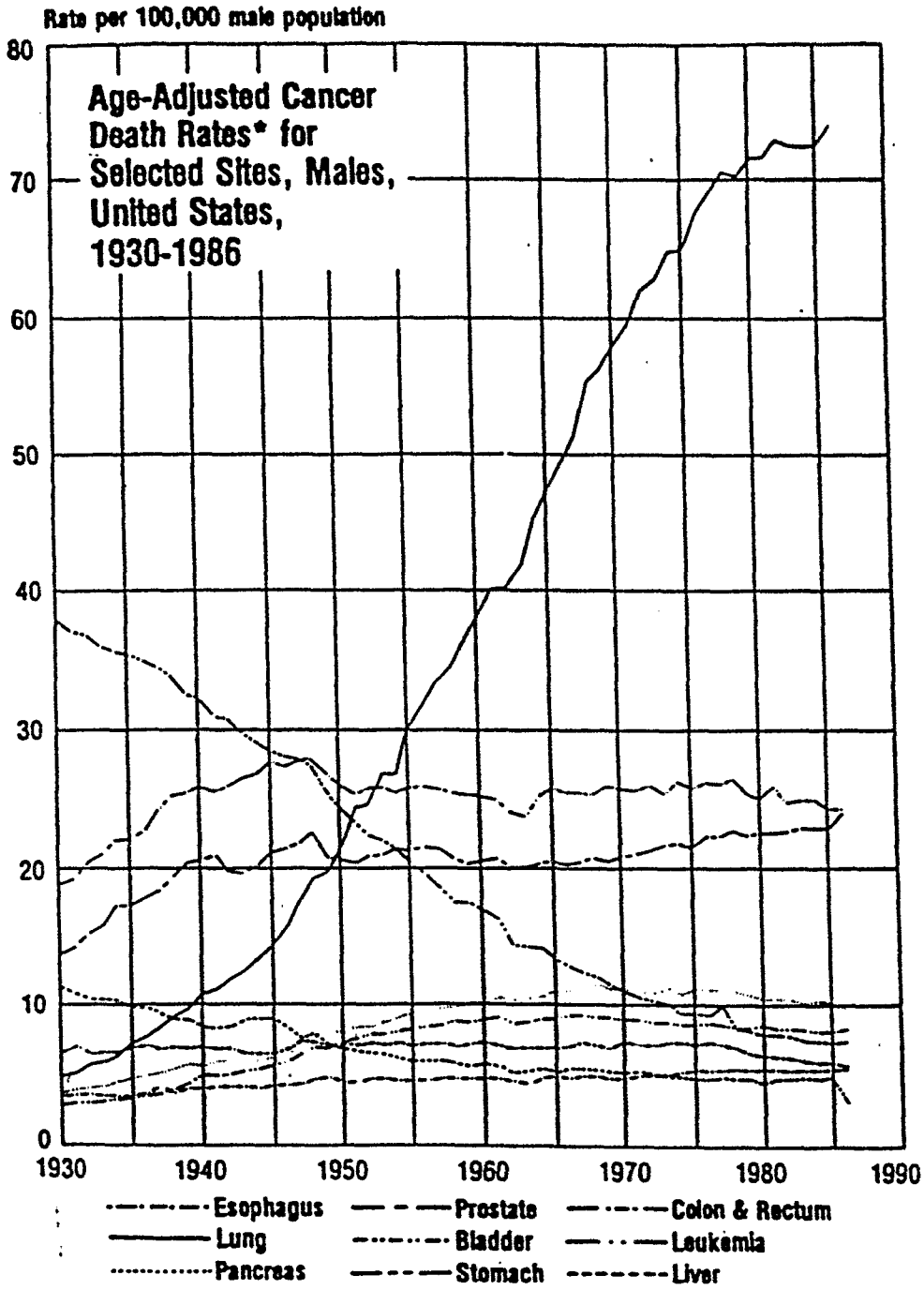

Figure 4-1. Age-adjusted cancer death rates* for selected sites, males, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

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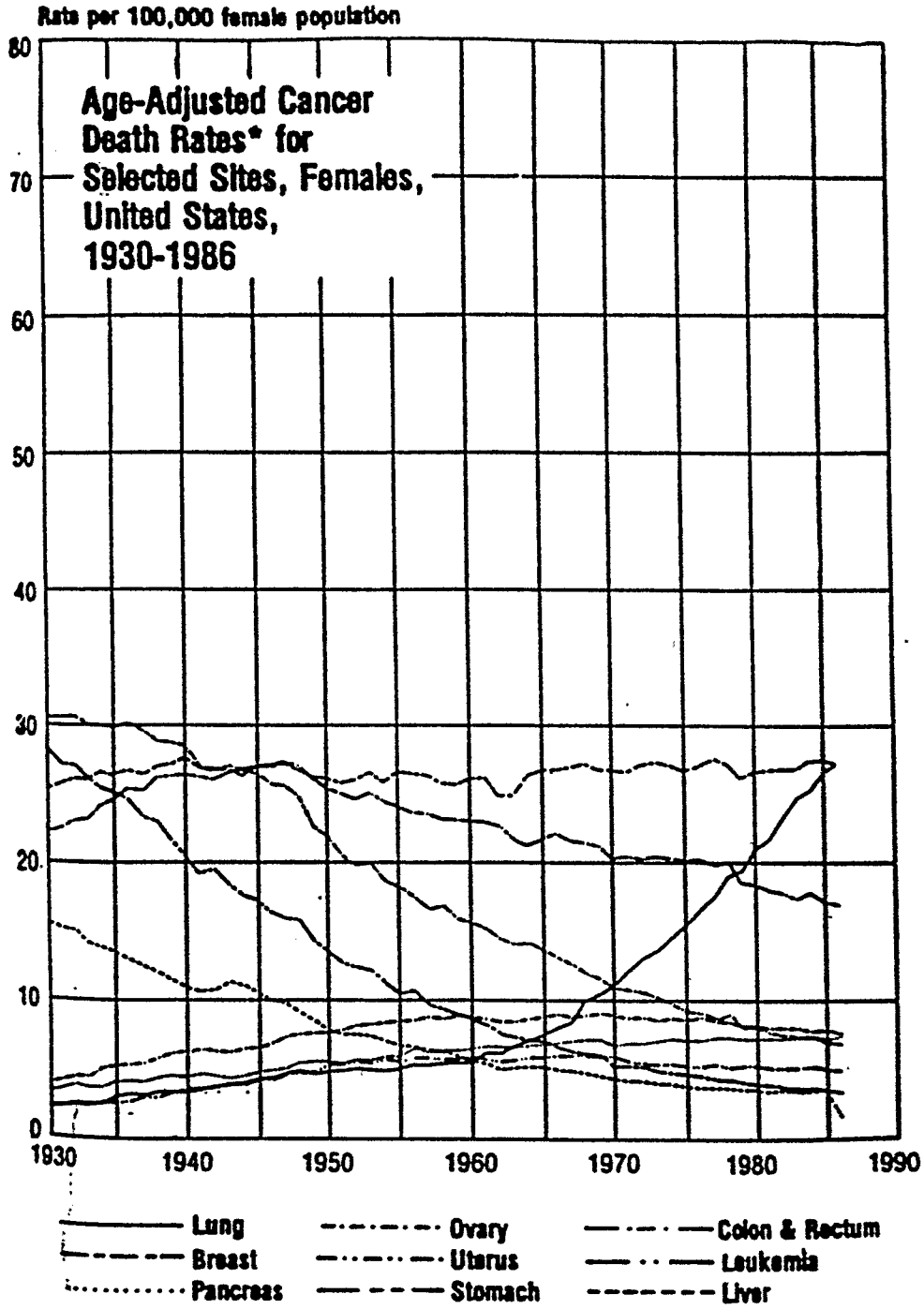

Figure 4-2. Age-adjusted cancer death rates* for selected sites, females, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

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4.2.2. Dose-Response Relationships

More than 50 independent retrospective studies have consistently found a dose-related association between smoking and lung cancer (U.S. DHHS, 1982). Eight major prospective studies from five countries corroborate this association:

- American Cancer Society (ACS) Nine-State Study (white males) (Hammond and Horn, 1958a,b)
- Canadian War Veterans Study (Best et al., 1961; Lossing et al., 1966)
- British Doctors Study (Doll and Hill, 1964a,b; Doll and Peto, 1976; Doll et al., 1980)
- American Cancer Society 25-State Study (Hammond, 1966; Hammond and Seidman, 1980)
- U.S. Veterans Study (Kahn, 1966; Rogot and Murray, 1980)
- California Labor Union Study (Weir and Dunn, 1970)
- Swedish Study (sample of census population) (Cederlöf et al., 1975)
- Japanese Study (total population of 29 health districts) (Hirayama, 1967, 1975a,b, 1977, 1978, 1982, 1985).

Details of the designs of these studies are summarized in Table 4-1. These eight studies together represent more than 17 million person-years and more than 330,000 deaths. Lung cancer mortality ratios from the prospective studies are presented in Table 4-2. Combining the data from the prospective studies results in a lung cancer mortality ratio of about 10 for male cigarette smokers compared with nonsmokers. (Note that these lung cancer mortality ratios underestimate the relative risk of lung cancer to smokers compared with a non-tobacco-smoke-related background risk to nonsmokers [see Chapter 6], given the causal association between ETS exposure and lung cancer in nonsmokers documented in this report.)

This strong association between smoking and lung cancer is further enhanced by very strong and consistent dose-response relationships. A gradient of increasing risk for lung cancer mortality with increasing numbers of cigarettes smoked per day was established in every one of the prospective studies (Table 4-3). Lung cancer mortality ratios for male smokers who smoked more than 20 cigarettes daily were generally 15 to 25 times greater than those for nonsmokers. Marked increases in lung cancer mortality ratios were also seen in all the lowest dose categories. Males who smoked fewer than 10 cigarettes per day had lung cancer mortality ratios 3 to 10 times greater than those for nonsmokers. There is no evidence of a threshold level for the development of smoking-induced lung cancer in any of the studies.

Dose-response relationships with respect to the duration of smoking also have been well established. From the British male physicians study, Peto and Doll (1984) calculated that the

Table 4-1. Main characteristics of major cohort studies on the relationship between smoking and cancer

Study	Year of enrollment	Sample size; initial samples; in brackets, population for followup	Source of information on smoking (proportion of respondents)	Duration of followup and no. of deaths	Completeness of followup for mortality
ACS 9-state study	1952	204,547 men [187,783]	Self-administered questionnaire	44 months 11,870 deaths	98.9%
Canadian veterans study	1955-1956	207,397 subjects (aged 30+) [92,000]	Self-administered questionnaire (57% respondents)	6 years 9,491 deaths in men; 1,794 deaths in women	NA
British doctors study	1951	34,440 men (aged 20+)	Self-administered questionnaire (69% respondents)	20 years 10,072 deaths	99.7%
		6,194 women (aged 20+)	Self-administered questionnaire (60% respondents)	22 years 1,094 deaths	99%
ACS 25-state study	1959-1960	1,078,894 subjects, first followup: 440,558 men, 562,671 women (aged 35-84); second followup: 358,422 men, 483,519 women	Self-administered questionnaire	4.5 + 5 years 26,448 deaths in men; 16,773 deaths in women	97.4% in women 97.9% in men in first followup
U.S. veterans study	1954	293,958 men (aged 31-84) [248,046]	Self-administered questionnaire (85% respondents)	16 years 107,563 deaths	Almost 100% ascertainment of vital status; 97.6% of death certificates retrieved
California study	1954-1957	68,153 men (aged 35-64)	Self-administered questionnaire	5-8 years 4,706 deaths	NA

(continued on the following page)

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Table 4-1. (continued)

Study	Year of enrollment	Sample size; initial samples; in brackets, population for followup	Source of information on smoking (proportion of respondents)	Duration of followup and no. of deaths	Completeness of followup for mortality
Swedish study	1963	27,342 men, 27,732 women (aged 18-69)	Self-administered questionnaire (89% respondents)	10 years 5,655 deaths (2,968 autopsies)	NA
Japanese study	1965	122,261 men, 142,857 women (aged 40+)	Interview (95% of population in area)	16 years 51,422 deaths	Total

NA = not available.

Source: IARC, 1986.

Table 4-2. Lung cancer mortality ratios--prospective studies

Population	Size	Number of deaths	Nonsmokers	Cigarette smokers
British doctors study	34,000 males	441	1.00	14.0
	6,194 females	27	1.00	5.0
Swedish study	27,000 males	55	1.00	7.0
	28,000 females	8	1.00	4.5
Japanese study	122,000 males	940	1.00	3.76
	143,000 females	304	1.00	2.03
ACS 25-state study	358,000 males	2,018	1.00	8.53
	483,000 females	439	1.00	3.58
U.S. veterans study	290,000 males	3,126	1.00	11.28
Canadian veterans study	78,000 males	331	1.00	14.2
ACS 9-state study	188,000 males	448	1.00	10.73
California males in 9 occupations	68,000 males	368	1.00	7.61

Source: U.S. DHHS, 1982.

Table 4-3. Lung cancer mortality ratios for men and women, by current number of cigarettes smoked per day--prospective studies

	Men		Women	
Population	Cigarettes smoked per day	Mortality ratios	Cigarettes smoked per day	Mortality ratios
ACS 25-state study	Nonsmoker	1.00	Nonsmoker	1.00
	1-9	4.62	1-9	1.30
	10-19	8.62	10-19	2.40
	20-39	14.69	20-39	4.90
	40+	18.71	40+	7.50
British doctors study	Nonsmoker	1.00	Nonsmoker	1.00
	1-14	7.80	1-14	1.28
	15-24	12.70	15-24	6.41
	25+	25.10	25+	29.71
Swedish study	Nonsmoker	1.00	Nonsmoker	1.00
	1-7	2.30	1-7	1.80
	8-15	8.80	8-15	11.30
	16+	13.70	16+	--
Japanese study (all ages)	Nonsmoker	1.00	Nonsmoker	1.00
	1-19	3.49	<20	1.90
	20-39	5.69	20-29	4.20
	40+	6.45		
U.S. veterans study	Nonsmoker	1.00		
	1-9	3.89		
	10-20	9.63		
	21-39	16.70		
	≥40	23.70		
ACS 9-state study	Nonsmoker	1.00		
	1-9	8.00		
	10-20	10.50		
	20+	23.40		
Canadian veterans study	Nonsmoker	1.00		
	1-9	9.50		
	10-20	15.80		
	20+	17.30		
California males in 9 occupations	Nonsmoker	1.00		
	about ½ pk	3.72		
	about 1 pk	9.05		
	about 1½ pk	9.56		

Source: U.S. DHHS, 1982.

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excess annual incidence rates of lung cancer after 45, 30, and 15 years of cigarette smoking were in the approximate ratio of 100:20:1 to each other. The California and Swedish studies also demonstrated an increasing risk of lung cancer in men with longer smoking duration (Table 4-4).

Four of the prospective studies examined lung cancer mortality in males by age at initiation of smoking and found increasing risk with younger age (Table 4-5). Some of the studies also investigated smoking cessation in men and observed a decrease in lung cancer risk with increasing number of years since quitting smoking (Table 4-6). The Cancer Prevention Study II, a study of 1,200,000 people in all 50 states, reveals a similar trend for women who quit smoking (Figure 4-3). The occurrence of higher lung cancer mortality ratios in the groups with only a few years since cessation as compared with current smokers (Table 4-6 and Figure 4-3) is attributable to the inclusion of recent ex-smokers who were forced to stop smoking because they already had smoking-related symptoms or illness (U.S. DHHS, 1990a). The increased lung cancer risks seen in people who started smoking at a younger age and the decreased risks seen with time since smoking cessation suggest both initiation and promotion capabilities of tobacco smoke components.

Additional dose-response relationships have been derived from consideration of the types of tobacco products used. Pipe and cigar smokers, who inhale less deeply than cigarette smokers, have lower risks of lung cancer than cigarette smokers (Table 4-7). Furthermore, the American Cancer Society 25-state study found decreased risks for lung cancer in males and females who smoked cigarettes with lower tar and nicotine content compared with those who smoked cigarettes with higher tar and nicotine content (Table 4-8), although these decreased risks are still substantially higher than the risk to nonsmokers. Similarly, it has been established that smokers of filtered cigarettes have relatively lower lung cancer risks than smokers of nonfiltered cigarettes (Table 4-9). Filters reduce the amount of tars, and hence a portion of the carcinogenic agents, in the MS inhaled by the smoker. Passive smokers, however, do not share in any benefit derived from cigarette filters (see Chapter 3) and may, in fact, be exposed to greater amounts of ETS if smokers of filtered cigarettes smoke a greater number of cigarettes to compensate for any reduction in nicotine uptake resulting from the filters (U.S. DHHS, 1986).

4.2.3. Histological Types of Lung Cancer and Associations With Smoking

A number of epidemiologic studies have also examined the association between various histological types of lung cancer and smoking. The results of some of these investigations are summarized in Table 4-10. Problems in interpreting the results of such studies include differences in the nomenclature, criteria, and verification of tumor classification; inadequacy of some specimens; and the small size of many of the patient groups, resulting in unstable risk

Table 4-4. Relationship between risk of lung cancer and duration of smoking in men, based on available information from cohort studies

Reference	Duration of smoking (years)	Standardized mortality ratio (no. of observed deaths)	Approximate annual excess death rate (%)[1]
Weir and Dunn (1970)	1-9	1.13	0.002 (0.001)
	10-19	6.45	0.09 (0.05)
	20+	8.66	0.12 (0.08)
	Nonsmokers	1.0	0
Cederlöf et al. (1975)	1-29	1.8 (5)	0.01 (0.008)
	>30	7.4 (23)	0.1 (0.06)
	Nonsmokers	1.0 (7)	0

[1]The mortality ratio among nonsmokers was assumed to be 15.6 per 100,000 per year, as in the American Cancer Society 25-state study. Figures in parentheses were computed by the IARC working group, applying the British doctors' mortality rate among nonsmokers (10.0/100,000 per year).

Source: IARC, 1986.

Table 4-5. Lung cancer mortality ratios for males, by age of smoking initiation--prospective studies

Study	Age of smoking initiation in years	Mortality ratio
ACS 25-state study	Nonsmoker	1.00
	25+	4.08
	20-24	10.08
	15-19	19.69
	Under 15	16.77
Japanese study	Nonsmoker	1.00
	25+	2.87
	20-24	3.85
	Under 20	4.44
U.S. veterans study	Nonsmoker	1.00
	25+	5.20
	20-24	9.50
	15-19	14.40
	Under 15	18.70
Swedish study	Nonsmoker	1.00
	19+	6.50
	17-18	9.80
	Under 16	6.40

Source: U.S. DHHS, 1982.

Table 4-6. Relationship between risk of lung cancer and number of years since stopping smoking, in men, based on available information from cohort studies

Reference	No. of years since stopping smoking	Mortality ratio (no. of observed deaths)
ACS 25-state study (Hammond, 1966)	1-19 cig./day	
	Current smokers	6.5 (80)
	<1	7.2 (3)
	1-4	4.6 (5)
	5-9	1.0 (1)
	10+	0.4 (1)
	Nonsmokers	1.0 (32)
	20+ cig./day	
	Current smokers	13.7 (351)
	<1	19.1 (33)
	1-4	12.0 (33)
	5-9	7.2 (32)
	10+	1.1 (5)
	Nonsmokers	1.0 (32)
Swedish study (Cederlöf et al., 1975)	<10	6.1 (12)
	>10	1.1 (3)
	Nonsmokers	1.0 (7)
British doctors study (Doll and Peto, 1976)	Current smokers	15.8 (123)
	1-4	16.0 (15)
	5-9	5.9 (12)
	10-14	5.3 (9)
	15+	2.0 (7)
	Nonsmokers	1.0 (7)
Rogot and Murray (1980)	Current smokers	11.3 (2,609)
	<5	18.8 (47)
	5-9	~7.5 (86)
	10-14	~5.0 (100)
	15-19	~5.0 (115)
	20+	2.1 (123)
	Nonsmokers	1.0 NA

NA = not available.

Source: IARC, 1986.

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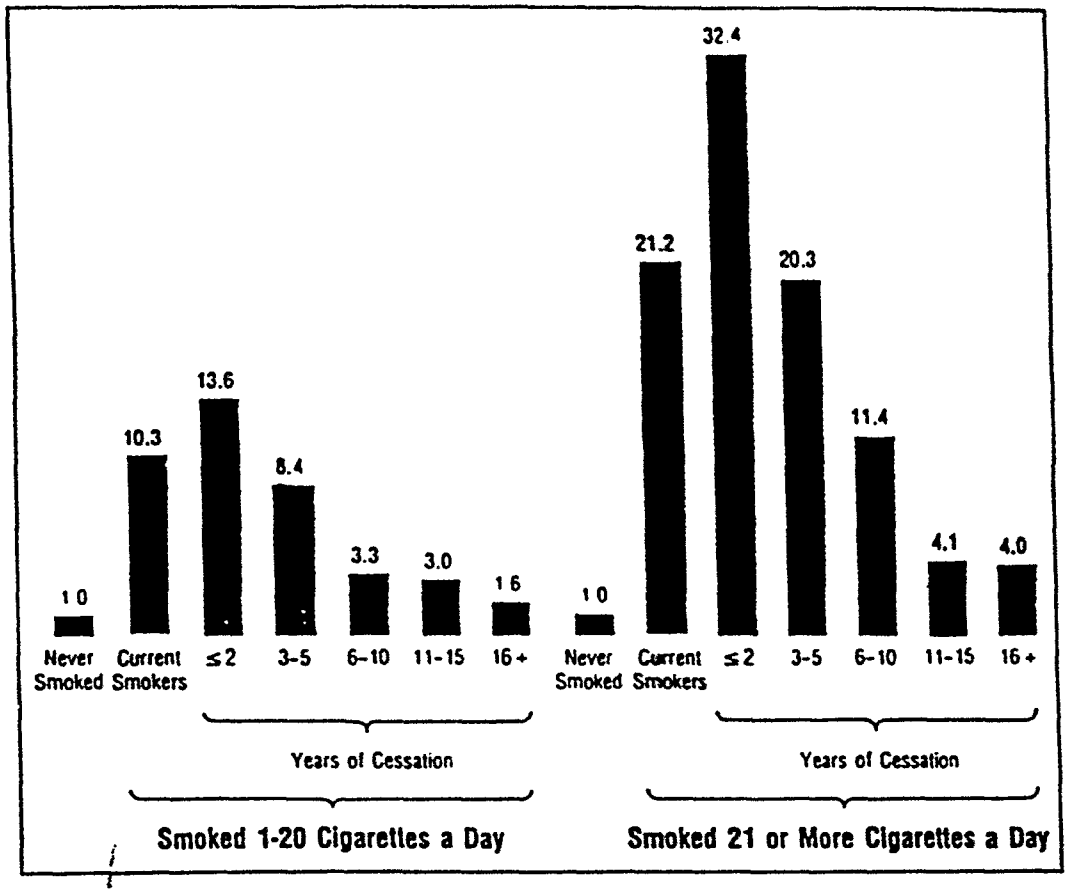

Figure 4-3. Relative risk of lung cancer in ex-smokers, by number of years quit, women, Cancer Prevention Study II.

Source: Garfinkel and Silverberg, 1991.

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Table 4-7. Relative risks of lung cancer in some large cohort studies among men smoking cigarettes and other types of tobacco

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
ACS 9-state study[1]	Never smoked	1.0	12.8	15
	Occasionally only	1.5	19.2	8
	Cigarettes only	9.9	27.2	249
	Cigars only	1.0	13.1	7
	Pipes only	3.0	38.5	18
	Cigarettes + other	7.6	97.7	148
	Cigars + pipes	0.6	7.3	3
Canadian veterans study	Nonsmokers	1.0		7
	Cigarettes only	14.9		325
	Cigars only	2.9		2
	Pipe only	4.4		18
	Ex-smokers	6.1		18
ACS 25-state study[1]	Never smoked	1.0	12	49
	Cigarettes only	9.2	111	719
	Cigars only	1.9	22	23
	Pipes only	2.2	27	21
	Cigarettes + other	7.4	89	336
	Cigars + pipes	0.9	11	11
Swedish study[1]	Nonsmokers	1.0		7
	Cigarettes only	7.0		28
	Cigarettes + pipe	10.9		27
	Pipe only	7.1		31
	Cigars only	9.2		6
	Ex-smokers	6.1		12

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Table 4-7. (continued)

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
British doctors study	Nonsmokers	1.0	10	
	Current smokers	10.4	104	
	Cigarettes only	14.0	140	
	Pipes and/or cigars only	5.8	58	
	Cigarettes + other	8.2	82	
	Ex-smokers	4.3	43	
U.S. veterans study[1]	Nonsmokers	1.0		2,609
	Cigarettes	11.3		1,095
	Cigarettes only	12.1		41
	Cigars only	1.7		32
	Pipes only	2.1		517
	Ex-cigarette smokers	4.0		
Norwegian study[1]	Nonsmokers	1.0		7
	Cigarettes	9.7		88
	Cigarettes only	9.5		70
	Pipes or cigars only	2.6		12
	Ex-smokers	2.8		11

[1]Figures given in original report.

Source: IARC, 1986.

Table 4-8. Age-adjusted lung cancer mortality ratios for males and females, by tar and nicotine (T/N) in cigarettes smoked

	Males	Females
High T/N[1]	1.00	1.00
Medium T/N	0.95	0.79
Low T/N	0.81	0.60

[1]The mortality rate for the category with highest risk was made 1.00 so that the relative reductions in risk with the use of lower T/N cigarettes could be visualized.

Source: U.S. DHHS, 1982.

Table 4-9. Relative risk for lung cancer by type of cigarette smoked (filter vs. nonfilter), in men, based on cohort and case-control studies

Reference	Type of study	Relative risk
Hawthorne and Fry (1978)	Cohort	0.8
Rimington (1981)	Cohort	0.7
Bross and Gibson (1968)	Case-control	0.6
Wynder et al. (1970)	Case-control	0.6
Dean et al. (1977)	Case-control	0.5

Source: IARC, 1986.

Table 4-10. Main results of studies dealing with the relationship between smoking and different histological types of lung cancer

Reference	Histological type	Results						Comments
Doll et al. (1957)		Sex	No. of cases	Relative risk Amount of tobacco smoked (g) <5	5-14	15-24	25+	Nonsmokers, 1.0 (RR) No. observed
	Kreyberg I	M	829	4.7	10.6	14.3	25.4	3
		F	32	1.0	1.7	8.3		16
	Kreyberg II	M	38	0.5	0.8	1.2	1.1	2
		F	8	1.1	2.3	4.1		5
Hammond and Horn (1958b)		Relative risk no. of packs/day						Nonsmokers, 1.0. Only regular smokers considered
		<½		½-1		1+		
	Adenocarcinoma	2.0		2.5		7.0		
	Other types	16.3		25.5		88.0		
Doll and Hill (1964a)		Death rate per 1,000 Amount of tobacco smoked (g)						Men only
		Ex-smokers		1-14	15-24	25+		
	Squamous-cell carcinoma	0.09		0.22	0.33	0.45		
	Small-cell and anaplastic carcinoma	0.05		0.10	0.20	0.38		
	Adenocarcinoma	0.03		0.03	0.12	0.07		

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Table 4-10. (continued)

Reference	Histological type	Results					Comments
Haenszel and Taeuber (1964)		Standardized mortality ratio					Women only; standardized mortality ratio; total group, 1.00
		Never-smokers	Ex-Smokers	Occasional cigarette smokers	Regular cigarette smokers		
					<1 pack/day	>1 pack/day	
	Adenocarcinoma	0.78	0.35	2.46	1.17	7.50	
	Squamous-cell and undifferentiated carcinoma	0.59	0.52	1.15	2.19	8.58	
Hanbury (1964)		No. of cases (%)					Women only
		"Heavy" and "medium" smokers		Nonsmokers and "remainder"			
	Small-cell carcinoma	18 (47)		21 (34)			
	Undifferentiated carcinoma	9 (24)		14 (23)			
	Squamous-cell carcinoma	9 (24)		12 (19)			
	Adenocarcinoma	2 (5)		15 (24)			

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Table 4-10. (continued)

Reference	Histological type	Results										Comments
Vincent et al. (1965)		Number of cigarettes smoked/day										Women only
		Total no. of cases	None		1-20		21-40		41+		Unknown	
			No.	%	No.	%	No.	%	No.	%	No.	%
	Squamous-cell carcinoma	19	10	53	3	16	2	10	2	10	2	10
	Small-cell carcinoma	17	2	12	7	41	6	35	2	12	0	0
	Adenocarcinoma	64	51	80	6	9	4	6	0	0	3	5
	Undifferentiated	22	12	54	4	18	6	27	0	0	0	0
	Others	41	32	78	8	20	1	2	0	0	0	0
		163	107	66	28	17	19	12	4	2	5	3
Wynder et al. (1970)		Sex	No. (%)									Heavy = 41+ cigarettes/day
			Cigarette smokers		Heavy smokers							
	Kreyberg I	M	191 (91.0)		59 (29.9)							
		F	24 (80.0)		3 (12.0)							
	Kreyberg II	M	61 (82.4)		9 (14.1)							
		F	21 (58.3)		1 (4.8)							
	Controls	M	199 (47.4)		26 (9.8)							
		F	53 (40.2)		3 (5.4)							

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Table 4-10. (continued)

Reference	Histological type	Results			Comments
Deaner and Trummer (1970)		Pack-years	Number of tumors	Smokers	
	Undifferentiated carcinoma	40	40	40 (100%)	
	Adenocarcinoma	12	19	13 (68%)	
	Squamous-cell carcinoma	52	9	9 (100%)	
Weiss et al. (1972)		Death rate per 1,000 man-years of observation (adjusted for age and race)			
		No. of cigarettes/day			
		1-10	10-19	20+	
	Squamous-cell carcinoma				
	Well differentiated	-	0.8	2.1	
	Poorly differentiated	0.7	0.4	1.0	
	Small-cell carcinoma	-	0.3	0.7	
	Adenocarcinoma	-	0.6	1.0	
Vincent et al. (1977)		No. of cigarettes smoked/day			
		0	1-20	21-40	41+	Other
	Squamous-cell carcinoma	14	219	110	120	16
	Adenocarcinoma	28	101	66	53	7
	Small-cell carcinoma	4	103	62	56	6
	Large-cell carcinoma	2	40	32	33	0
	Bronchiolo-alveolar carcinoma	6	20	9	6	0
	Mixed	0	9	5	5	0
	Other	6	30	19	17	4

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Table 4-10. (continued)

Reference	Histological type	Results							Comments
Chan et al. (1979)		Smoking category (kg tobacco smoked during lifetime)							Women only
			<100		100-199		>200		
		Non-smokers	Manufac-tured	All	Manufac-tured	All	Manufac-tured	All	
	Squamous-cell and small-cell carcinomas	1.0	3.6	3.4	3.7	4.2	2.6	4.1	
	Adenocarcinoma	1.0	1.9	1.4	1.4	1.8	1.6	1.7	
Joly et al. (1983)		Relative risk by duration of smoking (years)							Nonsmokers, 1.0
		Men				Women			
		1-29	30-39	40-49	50+	1-29	30-39	40-49	50+
	Squamous-cell carcinoma	15.0	15.9	39.5	42.2	4.4	9.4	31.4	51.9
	Adenocarcinoma	2.0	3.2	5.3	5.7	2.1	2.7	4.7	4.0
	Undifferentiated carcinoma	26.0	26.4	40.7	50.0	3.9	15.6	20.6	28.3
	Poorly differentiated carcinoma	6.4	7.7	10.8	10.2	3.2	7.8	5.6	13.1

Source: IARC, 1986.

estimates, particularly in women. There are four major histological types of lung cancer: squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma, and large-cell undifferentiated carcinoma. Sometimes two broad categories--Kreyberg Group I, containing squamous-cell and small-cell carcinomas, and Kreyberg Group II, containing all other epithelial lung cancers, including adenocarcinomas and large-cell undifferentiated carcinomas--are used for classification. The majority of the studies demonstrate an increase in the risk for lung cancer with increasing amount smoked for all four major histological groups in both males and females. The slope of the gradient for adenocarcinomas, however, is shallower than the slopes for the other types.

4.2.4. Proportion of Risk Attributable to Active Smoking

Table 4-11 presents data on the proportion of lung cancer deaths attributable to smoking in various countries. Differences by sex and between countries largely correlate with differences in the proportion of smokers within these populations and the duration and intensity of cigarette usage. In the early 1960s, 50% of U.S. men and 30% of U.S. women smoked, although these proportions have been declining in recent years (Garfinkel and Silverberg, 1991).

In the United States, deaths from lung cancer currently represent one-quarter of all cancer deaths. The American Cancer Society predicted there would be 143,000 lung cancer deaths in 1991 (Garfinkel and Silverberg, 1991). Over 85% of this lung cancer mortality is estimated to be attributable to tobacco smoking. In other words, the overwhelming majority of lung cancer deaths, which are a significant portion of all cancer deaths, result from smoking. The strong association between smoking and lung cancer and the dose-response relationships, with effects observable at low doses and no evidence of a threshold, make it highly plausible that passive smoking also causes lung cancer in humans.

4.3. LIFETIME ANIMAL STUDIES

The human evidence for the carcinogenicity of tobacco smoke is corroborated in experimental animal bioassays. The main animal evidence is obtained from inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of SS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments.

Negative responses in short-term animal studies (e.g., 60 to 90 days) are not reliable indicators of the carcinogenic potential of a compound because of the long latency period for cancer development. Long-term animal studies at or near the maximum tolerated dose level are used to ensure an adequate power for the detection of carcinogenic activity (U.S. EPA, 1986a).

Table 4-11. Lung cancer deaths attributable to tobacco smoking in certain countries

Country	Year	No. of deaths[1]	Expected deaths in nonsmokers[2]	Crude rate in persons aged 35+		AC[3]	AP[4]
				Observed	In non-smokers		
Canada							
Men	1978	6,435	556	142.8	11.8	5,762	0.9
Women	1978	1,681	487	34.0	9.9	1,194	0.71
England and Wales							
Men	1981	26,297	1,576	228.5	13.3	24,720	0.94
Women	1981	8,430	1,663	63.3	12.4	6,767	0.80
Japan							
Men	1981	16,638	2,868	64.8	10.7	13,184	0.83
Women	1981	6,161	2,593	21.0	8.9	3,568	0.58
Sweden							
Men	1981	1,777	301	85.0	14.0	1,476	0.83
Women	1981	654	281	28.0	12.3	373	0.57
USA							
Men	1979	72,803	5,778	166.7	12.7	67,024	0.92
Women	1979	25,648	5,736	50.0	11.1	19,912	0.78

[1]From the Global Epidemiological Surveillance and Health Situation Assessment data bank of WHO.
[2]Calculated by IARC, 1986. Slightly overestimates number of expected deaths.
[3]AC, number of cases attributable to smoking.
[4]AP, proportion of cases attributable to smoking.

Source: IARC, 1986.

4.3.1. Inhalation Studies

Although evidence of the carcinogenicity of cigarette smoke originated in humans, attempts were made to develop an inhalation model for smoking in experimental animals in order to study the carcinogenicity of various tobacco products. Such inhalation studies are difficult to conduct, however, because laboratory animals are reluctant to inhale cigarette smoke and will adopt shallow breathing patterns in response to aerosols and irritants. Furthermore, rodents are obligatory nose-breathers, and the anatomy and physiology of the respiratory tract and the biochemistry of the lung differ between rodents and humans. Because of these distinctions, laboratory animals and humans are likely to have different deposition and exposure patterns for the various cigarette smoke components in the respiratory system. For example, rodents have extensive and complex nasal turbinates where significant particle deposition could occur, decreasing exposure to the lung.

The Syrian golden hamster has been the most useful animal inhalation model found so far for studying smoking-induced carcinogenesis. It is more tolerant of tobacco smoke than mice and rats and is relatively resistant to respiratory infections. The hamster also has a low background incidence of spontaneous pulmonary tumors and is, in fact, refractory to the induction of lung cancers by known carcinogenic agents. The inhalation of tobacco smoke by the hamster does, however, induce carcinomas of the larynx. In one study (Dontenwill et al., 1973), three groups of 80 male and 80 female Syrian golden hamsters were exposed for 10 minutes to air-diluted cigarette smoke (1:15) once, twice, or three times daily, 5 days per week, for their lifetimes. Preinvasive carcinomas of the upper larynx were detected in 11.3%, 30%, and 30.6% of the animals, respectively, and invasive carcinomas were found in 0.6%, 10.6%, and 6.9%, respectively. No laryngeal tumors were observed in control animals. In another experiment, exposure for 59 to 80 weeks to an 11% or 22% cigarette smoke aerosol twice daily for 12 minutes resulted in laryngeal carcinomas in 3 of 44 and 27 of 57 animals, respectively, providing some evidence of a dose-response relationship for the induction of carcinoma of the larynx by cigarette smoke (Bernfeld et al., 1979). Bernfeld et al. suggest that the greater deposition of tar per unit of surface area in the larynx compared to the lung may explain the high yield of laryngeal cancers and lack of lung tumors in this animal model.

4.3.2. Intrapulmonary Implantations of Cigarette Smoke Condensates

Because of the difficulties with inhalation studies of cigarette smoke, some in vivo studies examine the carcinogenicity of cigarette smoke condensate (CSC) collected from smoking machines. CSC assays may not, however, reveal all of the carcinogenic activity of actual cigarette smoke, because these condensates lack most of the volatile and semivolatile components of whole

smoke. In lifetime rat studies, intrapulmonary implants of MS condensate in a lipid vehicle cause a dose-dependent increase in the incidence of lung carcinomas (Stanton et al., 1972; Dagle et al., 1978).

SS condensates have also demonstrated carcinogenicity when implanted into rat lungs (Grimmer et al., 1988). SS emitted by a smoking machine was separated into condensate fractions containing the semivolatiles, the polycyclic aromatic hydrocarbon (PAH)-free particulates and the PAHs with two or three rings, or the PAHs with four or more rings. These fractions were implanted into female Osborne-Mendel rats, following the procedure of Stanton et al. (1972), at a dose level of one cigarette per animal. At the end of the lifetime study, none of the 35 rats in each of the untreated control, vehicle control, or semivolatile-exposed groups had lung carcinomas. In the group exposed to the fraction containing PAH-free particulates and PAHs with 2 or 3 rings, there was 1 lung carcinoma in 35 animals. In the group exposed to the fraction comprising PAHs with 4 or more rings, there were 5 lung carcinomas in 35 rats. An additional group that was exposed to a dose of 0.03 mg benzo[a]pyrene (BaP) per rat exhibited 3 lung carcinomas in 35 animals. The condensate fraction containing BaP and the other PAHs with four or more rings from the SS generated by a single cigarette contains about 100 ng of BaP. Assuming a linear, nonsynergistic dose-response relationship, this would suggest that less than 1% of the total carcinogenicity of that condensate fraction can be attributed to the BaP present in the smoke.

4.3.3. Mouse Skin Painting of Cigarette Smoke Condensates

In addition, numerous studies have shown that when MS condensate suspended in acetone is chronically applied to mouse skin, significant numbers of the mice develop papillomas or carcinomas at the site of application (e.g., Wynder et al., 1957; Davies and Day, 1969). Mouse skin studies have also demonstrated that MS condensate has both tumor-initiating and tumor-promoting capabilities (Hoffman and Wynder, 1971).

One mouse skin painting study examined the carcinogenicity of SS condensate (Wynder and Hoffman, 1967). Cigarette tar from SS deposited on the funnel of a smoking machine was suspended in acetone and administered to mouse skin. Fourteen of thirty mice developed skin papillomas, and 3 of 30 developed carcinomas. In a parallel assay in the same study, a suspension of MS condensate applied to deliver a comparable amount of condensate to the skin of 100 mice yielded benign skin tumors in 24 and malignant tumors in 6 of the mice. This suggests that the condensate of SS has greater mouse skin tumorigenicity per unit weight than that of MS.

4.4. GENOTOXICITY

Supportive evidence for the carcinogenicity of tobacco smoke is provided by the demonstration of genotoxicity in numerous short-term assays. Extensive reviews of these studies can be found in IARC (1986) and DeMarini (1983); only the highlights are presented here. A few studies deal with whole smoke, but most examine CSC. Tobacco smoke is genotoxic in virtually every in vitro system tested, providing overwhelming supportive evidence for its carcinogenic potential.

In *Salmonella typhimurium*, for example, Basrur et al. (1978) found that both whole MS and MS condensates from various types of tobacco were mutagenic in the presence of a metabolic activating system. SS (Ong et al., 1984) and extracts of ETS collected from indoor air (Löfroth et al., 1983; Alfheim and Ramdahl, 1984; Lewtas et al., 1987; Ling et al., 1987; Löfroth et al., 1988) also exhibit mutagenic activity in this bacterium. Claxton et al. (1989) found that SS accounted for approximately 60% of the total *S. typhimurium* mutagenicity per cigarette--40% from the SS particulates and 20% from the semivolatiles. The highly volatile fraction, from either MS or SS, was not mutagenic.

Similarly, cigarette smoke produced mitotic gene conversion, reverse mutation, and reciprocal mitotic recombination in fungi (Gairola, 1982). In addition, CSC's induce mutations, sister chromatid exchanges, and cell transformation in various mammalian cells in culture. Putnam et al. (1985) demonstrated dose-dependent increases in sister chromatid exchange frequencies in bone-marrow cells of mice exposed to cigarette smoke for 2 weeks.

4.5. SUMMARY AND CONCLUSIONS

Lung cancer mortality rates have increased dramatically over the past 60 years in males, and, more recently, in females, with increasing cigarette consumption. High relative risks for lung cancer, associated with the number of cigarettes smoked per day, have been demonstrated in countless studies, with no evidence of a threshold level of exposure. Active smoking induces all four major histological types of human lung cancer--squamous-cell carcinomas, small-cell carcinomas, large-cell carcinomas, and adenocarcinomas--all in a dose-related manner. Dose-response relationships have also been established with respect to duration of smoking. Furthermore, lung cancer risk increases with the younger the age at initiation of smoking and decreases with the longer the time since cessation of smoking. These latter trends, coupled with evidence from mouse skin painting studies, suggest that tobacco smoke has both tumor-initiating and tumor-promoting capabilities.

Inhalation studies in hamsters confirm that MS is carcinogenic to the respiratory tract. In addition, mouse skin painting experiments and intrapulmonary implantations in rats have demonstrated the carcinogenicity of condensates from both MS and SS (the primary component of ETS), with SS condensate having a greater potency than MS condensate in mouse skin painting studies. Numerous genotoxicity tests contribute supporting evidence for the carcinogenic potential of MS and SS smoke and smoke condensates. The mutagenicity of ETS and its extracts has also been established. One study found that SS accounted for 60% of the total mutagenicity per cigarette.

As discussed in Chapter 3, MS and ETS are qualitatively similar in composition, and both contain numerous known or suspected human carcinogens. ETS constituents include essentially all of the same carcinogens found in MS, and many of these appear in greater amounts in SS, and hence, in ETS, than in MS, per unit of tobacco burned. This quantitative comparison is consistent with the observation noted above that SS condensates apparently have even greater carcinogenic potential than MS condensates.

The unequivocal causal association between tobacco smoking and lung cancer in humans with dose-response relationships extending down to the lowest exposure categories, as well as the corroborative evidence of the carcinogenicity of both MS and ETS provided by animal bioassays and in vitro studies and the chemical similarity between MS and ETS (Chapter 3), clearly establish the plausibility that ETS is also a human lung carcinogen. In addition, biomarker studies verify that passive smoking results in detectable uptake of tobacco smoke constituents by nonsmokers, affirming that ETS exposure is a public health concern (Chapter 3).

In fact, these observations are sufficient in their own right to establish the carcinogenicity of ETS to humans. According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The *Guidelines* establish "three criteria (that) must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

Given the strong dose-related associations, with high relative risks consistently observed across numerous independent studies from several countries, and the biological plausibility provided by ancillary evidence of the genotoxicity and animal carcinogenicity of MS and by

knowledge of the existence of many specific carcinogenic components within MS, confounding, bias, and chance can all be ruled out as possible explanations for the observed association between active smoking and lung cancer. Therefore, under the EPA carcinogen classification system, MS would be categorized as a Group A (known human) carcinogen. Furthermore, the extensive chemical and toxicological similarities between SS and MS, detailed in Sections 3.2, 4.3, and 4.4, strongly infer that SS is also capable of causing lung cancer in humans, as was documented for MS in Section 4.2. Thus, under EPA's carcinogen classification system, SS also belongs in Group A. Finally, because ETS is composed of SS and exhaled MS, and because ETS is known to be inhaled and absorbed into the body (Section 3.3.2), ETS would similarly be categorized as a Group A carcinogen.

In addition, there exists a vast body of epidemiologic data dealing specifically with lung cancer and exposure to ETS. These data should also be examined in the interest of weighing all the available evidence, as recommended by EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a), both for hazard identification and exposure-response assessment. The rapid dilution of both SS and exhaled MS into the environment and changing phase distributions of ETS components over time raise some questions about the carcinogenic potential of ETS under actual environmental exposure conditions. Furthermore, while MS and ETS may be qualitatively comparable, active smoking data do not constitute a good basis for quantitative estimation of the health effects of passive smoking because the relative uptake and deposition between active and passive smokers of the agent(s) responsible for these effects are not known (see Chapters 2 and 6). Provided the epidemiologic studies are of sufficient power and adequate study design, this database can offer unique information on the actual lung cancer risk to nonsmokers from exposure to true ambient levels of ETS. The epidemiologic evidence for the human lung carcinogenicity associated specifically with ETS is the subject of Chapter 5. These epidemiologic data are then used as the basis for the calculation of population risk estimates for lung cancer from passive smoking in Chapter 6.

5. HAZARD IDENTIFICATION II: INTERPRETATION OF EPIDEMIOLOGIC STUDIES ON ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER

5.1. INTRODUCTION

The Centers for Disease Control attributed 434,000 U.S. deaths in 1988 to smoking (CDC, 1991a). Major disease groups related to smoking mortality include lung cancer, chronic obstructive pulmonary disease, coronary heart disease, and stroke, with smoking accountable for an estimated 87%, 82%, 21%, and 18% of total deaths, respectively. Lung cancer alone accounted for about 25% to 30% of the total smoking mortality, with some 100,000 deaths. The age-standardized annual lung cancer mortality rates for 1985 are estimated at 12 per 100,000 for females and 15 per 100,000 for males who never smoked but 130 per 100,000 for female cigarette smokers and 268 per 100,000 for male cigarette smokers, a relative risk of 10.8 and 17.4, respectively (Garfinkel and Silverberg, 1991).

Chapter 4 discusses the biological plausibility that passive smoking also may be a risk factor for lung cancer because of the qualitative similarity of the chemical constituency of sidestream smoke, the principal source of environmental tobacco smoke (ETS), and mainstream smoke taken in during the act of "puffing" on a cigarette, and because of the apparent nonthreshold nature of the dose-response relationship observed between active smoking and lung cancer. Although the relative risk of lung cancer from passive smoking would undoubtedly be much smaller than that for active smoking, the ubiquity of ETS exposure (Chapter 3) makes potential health risks worth investigating.

This chapter analyzes the data from the large number of epidemiologic studies on ETS and lung cancer that contain data on the effects of ETS on never-smoking women. Although some of the studies involve male nonsmokers and former smokers of both sexes, the female never-smokers comprise the large majority of the database--more than 3,000 cases and 6,000 controls in the 27 case-control studies and almost 300,000 female never-smokers followed in the 4 cohort studies. Whenever study data are separated by sex and smoking status, women never-smoker results are used. The use of a more homogeneous group allows more confidence in the results of combined study analyses. All of the studies used provide data on adult home exposure to ETS. Some also provide information on childhood and/or workplace exposure, but there is far less information on these exposures; therefore, in order to develop one large database for analysis, only the female exposures from spousal smoking are considered. The exposure surrogate used is a report of the husband's smoking status. Wherever a measure of the amount of exposure to husband's smoking is available, additional analyses are performed to examine effects in the highest exposure groups (Section 5.3.3.2) and dose-response relationships (Section 5.3.3.3). Virtually all of the 31 studies

available classify never-smoking women as "exposed" or "unexposed" to ETS based on self- or proxy-reported smoking in the subject's environment, usually according to whether or not a woman is married to a smoker. In addition, 17 studies provide sufficient information for highest exposure group and exposure-response analyses. Other analyses of the data include adjusting for the potential upward bias of smoker misclassification (Section 5.2.2); examining confounders, effect modifiers, and sources of potential bias (Section 5.4); and pooling qualitatively higher ranked studies (Section 5.5). It is hoped that by analyzing the data in several different ways, a clear picture will emerge (Section 5.6).

Throughout this chapter, one-tailed tests of significance ($p = 0.05$) are used, which increases the statistical ability (power) to detect an effect. The 90% confidence intervals used for the analyses performed are consistent with the use of the one-tailed test. The justification for this usage is based on the *a priori* hypothesis (from the plausibility of a lung cancer effect documented in Chapters 3 and 4) that a positive association exists between exposure to ETS and lung cancer.

Epidemiologic evidence of an association between passive smoking and lung cancer first appeared 10 years ago in a prospective cohort study in Japan (Hirayama, 1981a) and a case-control study in Greece (Trichopoulos et al., 1983). Both studies concluded that the lung cancer incidence and mortality in nonsmoking women was higher for women married to smokers than for those married to nonsmokers. Although there are other sources of exposure to ETS, particularly outside the home, the assumption is that women married to smokers are exposed to more tobacco smoke, on average, than women married to nonsmokers. These two studies, particularly the cohort study from Japan, evoked considerable critical response. They also aroused the interest of public health epidemiologists, who initiated additional studies.

At the request of two Federal agencies--the U.S. Environmental Protection Agency (Office of Air and Radiation) and the U.S. Department of Health and Human Services (Office of Smoking and Health)--the National Research Council (NRC) formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on the health consequences. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail and includes summary analyses of the evidence from 10 case-control and 3 cohort (prospective) studies. It concludes, "Considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers."

The NRC committee was particularly concerned about the potential bias in the study results caused by the fact that current and former smokers may have incorrectly reported themselves as lifelong nonsmokers (never-smokers). Using reasonable assumptions for misreported smoking habits, the committee determined that a plausible range for the true relative

risk is 1.15 to 1.35, with 1.25 the most likely value. When these relative risks also are corrected for background exposure to ETS to make the risk relative to a baseline of zero ETS exposure, the resultant estimate is 1.42, with a plausible range of 1.24 to 1.61.

Two other major reports on passive smoking have appeared: the Surgeon General's report on the health consequences of passive smoking (U.S. DHHS, 1986) and the report on methods of analysis and exposure measurement related to passive smoking by the International Agency for Research on Cancer (IARC, 1987a). The Surgeon General's report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS lead to the conclusion that involuntary smoking is a cause of lung cancer.

The IARC committee emphasized issues related to the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. Included in the 1987 IARC report is a citation from the summary statement on passive smoking of a previous IARC report that the epidemiologic evidence available at that time (1985) was compatible with either the presence or absence of lung cancer risk. Based on other considerations related to biological plausibility, however, it concludes that passive smoking gives rise to some risk of cancer. Specifically, the report (IARC, 1986) states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive smoking," and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens . . . leads to the conclusion that passive smoking gives rise to some risk of cancer.

In the years since those reports, the number of studies available for analysis has more than doubled. There are now 31 epidemiologic studies available from eight different countries, listed in Table 5-1. Twenty-seven studies employ case-control designs, denoted by the first four letters of the first author's name for convenient reference, and four are prospective cohort studies, distinguished by the designation "(Coh)." Six case-control studies, FONT (USA), JANE (USA), KALA (Greece), LIU (China), SOBU (Japan), and WUWI (China), have been published as recently as 1990. The small cohort study from Scotland (Gillis et al., 1984) has been updated and is now included under the name HOLE(Coh); another small cohort study on Seventh-Day Adventists in the United States, an unpublished dissertation, is included as BUTL(Coh). The abstracts for a second case-control study by Kabat and Wynder and a new one by Stockwell and colleagues are included in Section A.4, but insufficient information is available to include their results.

Table 5-1. Epidemiologic studies on ETS and lung cancer in this report and tier ranking

Study	Tier[1]	Country	Within country	References
AKIB	2	Japan	Hiroshima	Akiba et al. (1986)
BROW	3	United States	Colorado	Brownson et al. (1987)
BUFF	3	United States	Texas	Buffler et al. (1984)
CHAN	4	Hong Kong		Chan and Fung (1982)
CORR	2	United States	Louisiana	Correa et al. (1983)
FONT	1	United States	Five metro areas	Fontham et al. (1991)
GAO	3	China	Shanghai	Gao et al. (1987)
GARF	2	United States	New Jersey, Ohio	Garfinkel et al. (1985)
GENG	4	China	Tianjin	Geng et al. (1988)
HUMB	2	United States	New Mexico	Humble et al. (1987)
INOU	4	Japan	Kanajawa	Inoue and Hirayama (1988)
JANE	2	United States	New York	Janerich et al. (1990)
KABA	2	United States	New York	Kabat and Wynder (1984)
KALA	1	Greece	Athens	Kalandidi et al. (1990)
KATA[2]		Japan		Katada et al. (1988)
KOO	1	Hong Kong		Koo et al. (1987)
LAMT	2	Hong Kong		Lam et al. (1987)
LAMW	3	Hong Kong		Lam (1985)
LEE	2	England		Lee et al. (1986)
LIU	4	China	Xuanwei	Liu et al. (1991)
PERS	1	Sweden		Pershagen et al. (1987)
SHIM	2	Japan	Nagoya	Shimizu et al. (1988)
SOBU	2	Japan	Osaka	Sobue (1990)
SVEN	2	Sweden	Stockholm	Svenson et al. (1989)

(continued on the following page)

Table 5-1. (continued)

Study	Tier	Country	Within country	References
TRIC	3	Greece	Athens	Trichopoulos et al. (1981, 1983)
WU	2	United States	California	Wu et al. (1985)
WUWI	4	China		Wu-Williams and Samet (1990)
BUTL(Coh)	2	United States	California	Butler (1988)
GARF(Coh)	3	United States		Garfinkel (1981)
HIRA(Coh)	2	Japan		Hirayama (1984)
HOLE(Coh)	1	Scotland	Paisley Renfrew	Hole et al. (1989)

[1]Tier rankings refer to this report's ratings of studies for utility of studying the association of ETS and lung cancer, where "1" is highest (see Section 5.5 and Section A.3).
[2]KATA has no tier number because the odds ratio cannot be calculated.

Because of coincidental timing, the 1986 reports of the Surgeon General and the NRC review approximately the same epidemiologic studies. More specifically, the NRC report includes nine of the studies shown in Table 5-1: AKIB, CHAN, CORR, GARF, KABA, KOO, LEE, PERS, and TRIC; WU was available but not included because the crude data were not reported. (Crude data consist of the number of exposed and unexposed subjects among lung cancer cases and controls, where a subject is typically classified as exposed to ETS if married to a smoker.) The NRC also excluded an earlier version of the KOO study and the studies by Knoth et al. (1983) (no reference population was given), Miller (1984) (did not report on lung cancers separately), and Sandler et al. (1985) (included very few lung cancers). Aside from WU, these studies also are omitted from this report for the same reasons.

Tables 5-2 and 5-3 provide an overview of some descriptive features of the individual ETS studies included in this report. The studies are grouped by country in Table 5-2, which indicates the time period of data collection in each study, sample size, and prevalence of ETS exposure for each study. The geographical distribution of the current epidemiologic evidence is diverse. By country, the number of studies and its percentage of the total number of studies over all countries is as follows: China (4, 13%), England (1, 3%), Greece (2, 6%), Hong Kong (4, 13%), Japan (6, 19%), Scotland (1, 3%), Sweden (2, 6%), and United States (11, 35%). (One of the

Table 5-2. Studies by location, time, size, and ETS exposure

Country	Study	Accrual[1] period	Size[2] Cases	Size[2] Controls	ETS exposure (%)[3] Cases	ETS exposure (%)[3] Controls
Greece	KALA	1987-89	90	116	71	60
Greece	TRIC	1978-80	40	149	73	52
Hong Kong	CHAN	1976-77	84	139	60	53
Hong Kong	KOO	1981-83	86	136	59	49
Hong Kong	LAMT	1983-86	199	335	58	45
Hong Kong	LAMW	1981-84	60[4]	144[4]	62[4]	44[4]
Japan	AKIB	1971-80	94	270	78	70
Japan	HIRA(Coh)	1965-81	— 91,540 —		— 76 —	
Japan	INOU	1973-83	22	47	82	64
Japan	SHIM	1982-85	90	163	58	56
Japan	SOBU	1986-88	144	731	56	54
USA	BROW	1979-82	19	47	21	15
USA	BUFF	1976-80	41	196	80	84
USA	BUTL(Coh)	1976-82	— 9,207[5] —		— 34[5] —	
USA	CORR	1979-82	22	133	64	46
USA	FONT	1985-88	420	780[6]	70	63[6]
USA	GARF	1971-81	134	402	67	61
USA	GARF(Coh)	1959-72	— 176,739 —		— 72 —	
USA	HUMB	1980-84	20	162	75	56
USA	JANE	1982-84	191	191	*[7]	60[7]
USA	KABA	1961-80	24	25	54	60
USA	WU	1981-82	29[8]	62[8]	*	*
W. Europe						
Scotland	HOLE(Coh)	1972-85	— 1,784 —		— 73 —	
England	LEE	1979-82	32	66	69	68

(continued on the following page)

Table 5-2. (continued)

Country	Study	Accrual[1] period	Size[2] Cases	Size[2] Controls	ETS exposure (%)[3] Cases	ETS exposure (%)[3] Controls
W. Europe (continued)						
Sweden	PERS	1961-80	67	*	49	*
Sweden	SVEN	1983-85	34	174	71	66
China	GAO	1984-86	246	375	77	74
China	GENG	1983	54	93	63	44
China	LIU	1985-86	54	202	83	87
China	WUWI	1985-87	417	602	49	55

[1]Time during which cases occurred.
[2]Number of subjects included in ETS analyses; where numbers differ for spousal smoking and other exposures, those for spousal smoking are given.
[3]Spousal smoking unless otherwise noted.
[4]Adenocarcinoma only. Data for all cell types were available only for general passive smoke exposure, which showed 77% of 75 cases and 56% of 144 controls exposed.
[5]Figure pertains to "spouse pairs" cohort, which is of principal interest regarding ETS; a subgroup of this cohort comprised the "ASHMOG" cohort.
[6]Figure is for population controls; study also included 351 colon cancer controls (66% exposed).
[7]ORs but no exposure prevalences are presented for spousal smoking in the source. The value shown for controls is taken from KABA, as closest to JANE in time and location; no exposure percentage is assumed for cases.
[8]Adenocarcinoma only. Analyses for other cell types included smokers while adjusting for smoking status.

*Data not available.

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Table 5-3. Case-control studies of ETS: characteristics

Study	Percentage proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
AKIB	90	88	70.2 35-95	* *	Atomic bomb survivor population	Age, sex, residence, vital status, med. subject[3]	No
BROW	69	39	66.3	68.2	Cancer cases[4]	Age, sex	No[5]
BUFF	82	76	30-79	30-79	Cancer cases[6]	Age, sex	No[5]
CHAN	*	*	39-70	39-70	Orthopedic patients	Matched but variables unspecified	No[5]
CORR	*	*	*	*	Hospital patients[7]	Age (± 5), sex, race	No[5]
FONT	34	0-10[8]	20-79	20-79	Cancer cases; general population	Age, (for cancer controls) race	Yes
GAO	0	*	35-69	35-69	General population	Age (± 5)	No[5]
GARF	88	*	≥40	≥40	Cancer cases[9]	Age (± 5), hospital	Yes
GENG	0	0	≤65	≤65	*	Age (± 2), sex, race, marital status	No[5]
HUMB	*	*	≤85	≤85	General population	Age (± 10), sex, ethnicity	No[5]
INOU	*	*	*	*	Cerebrovascular disease deaths	Age, year of death (± 2.5), district	No[5]
JANE	33[10]	33[10]	67.1[10]	68.1[10]	New York State Dept. of Motor Vehicles	Age, sex, county, smoking history	Yes

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Table 5-3. (continued)

Study	Percentage proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
KABA	0	0	61.6	53.9	Patients[11]	Age (± 5), sex, race, hospital	Yes
KALA	0	0	≥35	≥35	Orthopedic patients	Sex	Yes
KATA	0	0	67.8	*	Noncancer patients	Age (± 2), sex	Yes
KOO	0	0	*	*	"Healthy"[12]	Age (± 5), residence, housing	No[5]
LAMT	0	0	*	*	"Healthy"[13]	Age (± 5), residence	No[5]
LAMW	*	*	67.5	66	Hospitalized orthopedic patients	Age, socio-economic status, residence[14]	No[5]
LEE	38[15]	38	35-74	35-74	Patients[16]	Age, sex, hospital location, time of interview	No[5,17]
LIU	0	0	52	52	General population?	Age (± 2), sex, village	Yes
PERS	*[18]	*	*[19]	*	*[20]	Age (± 1), sex	Yes
SHIM	0	0	59 35-81	58 35-81	Patients[21]	Age (± 1), hospital, admission date	Yes
SOBU	0	0	60	56	Patients	None	No
SVEN	0	0	66.3		General population	Age	No[5]

(continued on the following page)

Table 5-3. (continued)

Study	Percentage proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
TRIC	0	0	62.8	62.3	Hospitalized orthopedic patients	Age, occupation, education[14]	No[5]
WU	0	0	<76	<76	Neighbor-hood[13]	Age (± 5), sex, race	No[5]
WUWI	0	0	55.9[22]	55.4[22]	General population	Sex, age[23]	No[5]

[1]"Ca" and "Co" stand for "cases" and "controls," respectively.
[2]Single values are the average or median. Paired values are the range.
[3]Participation in RERF biennial medical examination program.
[4]Persons with cancers of bone marrow or colon in Colorado Control Cancer Registry.
[5]Not matched on personal smoking status (e.g., smoker/nonsmoker).
[6]Population-based and decedent comparison subjects selected from state and Federal records.
[7]Assorted ailments.
[8]0% for general population and 10% for colon cancer controls.
[9]Colorectal cancer.
[10]Includes males and females and long-term ex-smokers.
[11]Diseases not related to smoking.
[12]Selected from a healthy population.
[13]Living in neighborhood of matched case.
[14]"Similar" but not actually matched.
[15]Applies only to the 143 patients in the followup study.
[16]Excluding lung cancer, chronic bronchitis, ischemic heart disease, and stroke.
[17]Ongoing study modified for passive smoking.
[18]No overall percentages given.
[19]Two control groups: 15 to 65 and 35 to 85 for both cases and controls in groups 1 and 2, respectively.
[20]Two control groups were randomly chosen from the cohort under study.
[21]Patients in the same or adjacent wards with other diseases.
[22]Entire study population, including smokers.
[23]Frequency matched by 5-year age group to age distribution of cases reported in study area 2 years prior to initiation of study.

*Data not available.

studies from Japan, KATA, does not appear in most of the tables because the odds ratio cannot be calculated.) The studies differ by size, however, which has to be taken into account in analysis. There are two large cohort studies, GARF(Coh) and HIRA(Coh), conducted in the United States and Japan, respectively, and two very small ones, BUTL(Coh) and HOLE(Coh), from the United States and Scotland, respectively. There are two exceptionally large case-control studies--FONT and WUWI of the United States and China; the first was designed specifically to assess the association between ETS and lung cancer, whereas the second has broader exploratory objectives.

The accrual periods of the case-control studies are typically 2 to 4 years in length (exceptions with longer periods are AKIB [9 years], INOU [10 years], GARF [10 years], KABA [19 years], and PERS [9 years]) and occur between the early 1970s and late 1980s (exceptions are KABA [1961-1980] and PERS [1961-1980]). The two large cohort studies were conducted relatively early (GARF(Coh), 1959-72; HIRA(Coh), 1965-81). Differences in study duration or accrual period should not be consequential for hazard identification, which is the topic addressed in this chapter, but both factors affect the estimation of population risk (Chapter 6). Earlier study results are more uncertain for projection of current risk, and parameter values used for modeling are more uncertain when based on extended study periods. Table 5-2 also demonstrates variability across studies in the percentages of cases and controls classified as exposed to ETS. For example, at the extremes for U.S. studies alone, BUFF and BROW classify 84% and 15% of controls as exposed to ETS, respectively. Statistical variability and differences across subpopulations sampled are partially explanatory, but a major factor is differences between researchers' criteria for classification of subjects as exposed to ETS. This issue affects study comparability and observed values of relative risks, which affect both hazard identification and characterization of population risk.

Another example of a study feature of broad consequences in both case-control and cohort studies is the method of diagnosis or confirmation of lung cancer and exclusion of secondary lung cancers in subjects classified as having lung cancer, as shown in Table 5-4. Accurate classification of subjects vis-a-vis the presence or absence of primary lung cancer is essential to the validity of results; inaccurate classification can reduce the chance of detecting a positive association between ETS exposure and lung cancer, if it exists, by biasing the observed relative risk toward unity. (*Note*: "Relative risk" is used to mean the estimate of the true [but unknown] relative risk. For case-control studies, the estimate used is the odds ratio. For editorial convenience, "relative risk" is used for both case-control and cohort studies.)

The large majority of the studies (27 of 31 total) are of the case-control type, which are subject to more potential sources of bias than the cohort studies (see discussion in Section 5.4.1).

Table 5-4. Diagnosis, confirmation, and exclusion of lung cancer cases

Study	Diagnosis/Confirmation (%)[1] Histology		Cytology	Radio./ clinical	Other/ unspec.	Excluded secondary LC[2]
AKIB[3]	53		4	43	0	Y
BROW	———	100	———			Y
BUFF[3,4]	———	100	———			Y
CHAN[3,4]	82				18	N
CORR[3]	97				3	Y
FONT	100					Y
GAO[3,5]	43		38	19	10	Y
GARF[6]	100					Y
GENG[3]	85			4	11	N
HUMB[6,7]	———	83	———		17	Y
INOU	*		*	*	*	N
JANE[3]	99			1		Y
KABA	100					Y
KALA	48		38		14	Y
KATA	100					N
KOO	94				6	Y
LAMT	———	100	———			Y
LAMW	———	100	———			Y
LEE	*		*	*	*	N
LIU[8]	———	17	———	83	0	N
PERS	83		16		1	Y
SHIM	100					Y
SOBU	100					Y
SVEN[3]	70		29		1	Y
TRIC[3]	28		37	35		N
WU	100					Y
WUWI[3]	42		32	26		Y
BUTL(Coh)[9]		100				Y
GARF(Coh)	*		*	*		N

(continued on the following page)

Table 5-4. (continued)

Study	Diagnosis/Confirmation (%)[1] Histology	Cytology	Radio./ clinical	Other/ unspec.	Excluded secondary LC[2]
HIRA(Coh)	*	*	*		N
HOLE(Coh)[10]	*	*	*		N

[1]Figures apply to confirmation of original diagnosis when conducted.
[2]Y (for "yes") if specifically indicated; otherwise, N (for "no").
[3]Not restricted to never-smokers (contains former smokers or ever-smokers).
[4]Inconsistency in article. May be 100% histology.
[5]Diagnostic information was reviewed for study.
[6]Includes males.
[7]Available histologic specimens (17 cases) reviewed by pathologists. Poor agreement between review diagnoses and original cancer registry diagnoses (8 of 17 cases). Only reviewed cases, however, are presented in article.
[8]Includes male ever- and never-smokers and one female ever-smoker (control).
[9]Includes one former smoker.
[10]Death certificate diagnosis checked against Scottish cancer registry records.

*Data not available.

To continue the overview depicting some basic similarities and differences between studies that may affect analysis of their results, some additional characteristics of the case-control studies alone are summarized in Table 5-3. The percentage of proxy response is high for some studies, but there is little basis for assessing the direction or magnitude of potential bias from this source. The age range of subjects differs across studies, but there is insufficient information on age distributions within studies to evaluate the effect of age or to adjust for differences between studies. The source of control subjects is a potential source of bias in some studies.

The table heading "ETS sample matched" refers to whether design matching applies to the ETS subjects (the never-smokers used for ETS/lung cancer analysis). As indicated under "matched variables," controls are virtually always matched (or at least similar) to cases on age and usually on several other variables as well that the researcher suspects may affect comparability of cases and controls. The matching often refers to a larger data set than the ETS subjects only, however, because many studies included smokers and investigated a number of issues in addition to whether passive smoking is associated with lung cancer. When the data on ETS subjects are

extracted from the larger data set, matching is not retained unless smoking status was one of the matching variables.

Although matching is commonly used as a method to reduce potential confounding, effective techniques also may be implemented during analysis of the data (e.g., the use of poststratification or logistic regression adjustment for unmatched, stratified, or frequency-matched samples). Use of a method of analysis that adjusts for known or suspected confounders and factors that may interact with ETS exposure to affect risk of lung cancer is particularly important for studies that are not designated as "ETS sample matched" in Table 5-3. Even with matched data, a method of analysis that controls for confounding, such as the use of matched pairs or regression techniques, is preferable. In fact, Breslow and Day (1980, p. 32) describe the main purpose of matching in a case-control study as permitting use of efficient analytical methods to control confounding by the factors used for matching.

The analysis for hazard identification in this report follows two approaches. The first approach (Section 5.3) treats all studies equally, i.e., statistical methods are applied to all studies without regard to differences in study utility for the task of hazard identification. Differences in study size, of course, are taken into account by the statistical methods. Statistical inference includes estimation, with confidence intervals, and hypothesis testing for an effect (an increased relative risk in ETS-exposed subjects) and for an upward trend (an increase in relative risk as some measure of ETS exposure increases). The second approach (Section 5.5) is motivated by the heterogeneity of the study evidence, as described above. Study size aside, some studies have higher utility than others for assessing questions related to ETS and lung cancer and thus should be given more weight. To implement this extended data interpretation, all studies are first reviewed individually for sources of bias and confounding that might affect interpretation of results for assessing ETS and lung cancer and then assigned a tier number from 1 to 4 accordingly. Tier 1 contains those studies of greatest utility for investigating a potential association between ETS and lung cancer. Other studies are assigned to Tiers 2, 3, and 4 as confidence in their utility diminishes. (*Note:* Study utility does not mean study quality. Utility is evaluated with respect to the research objectives *of this report*, while the objectives of individual studies often differ.) Pooled estimates of relative risk by country are then recalculated by tiers, beginning with the studies of highest utility (Tier 1) and adding studies from Tiers 2, 3, and 4 successively to see what effect a judgment of utility has on the overall outcome in each country. The criteria used in evaluating studies and the procedure for assigning them to tiers are described in Appendix A, which also contains the individual study reviews.

The selection of the most appropriate relative risk estimate to be used from each study is addressed in Section 5.2.1. In Section 5.2.2, each chosen relative risk estimate is adjusted downward to account for bias expected from some smokers misrepresenting themselves as nonsmokers. This topic has been a contentious issue in the literature for several years, with claims that this one source of systematic upward bias may account entirely for the excess risk observed in epidemiologic studies. Recent detailed investigation of this topic by Wells and Stewart (unpublished) make that claim unlikely (Appendix B). They found that a reasonable correction for bias, calculated on a study-by-study basis, is positive but small. Following this methodology, this report makes reductions in the relative risk estimates at the outset for each study individually before statistical inference or pooling estimates from studies of the same country. This is in contrast to the NRC report (1986), which makes the same downward adjustment to all studies (applied to an overall estimate of relative risk obtained after pooling all study estimates).

The estimates adjusted for smoker misclassification bias are the basis for statistical inference in Sections 5.3 (without regard to tier classification) and 5.5 (analysis by tier classification). Section 5.4 reviews the study results on potential modifying factors. Conclusions are then drawn for hazard identification (i.e., whether ETS is causally associated with increased lung cancer mortality) based on the total weight of evidence. Chapter 6 of this report addresses the upward adjustment on the U.S. relative risk estimate for background ETS exposures and the U.S. population risk of lung cancer from ETS.

5.2. RELATIVE RISKS USED IN STATISTICAL INFERENCE

5.2.1. Selection of Relative Risks

Two considerations largely affect the choice of relative risk (RR): (1) whether other relevant cofactors are taken into account (namely, potential confounders and risk modifiers that may be correlated with ETS exposure), and (2) the source and place of ETS exposure used. The alternatives (not yet adjusted for smoker misclassification) are shown by study in Tables 5-5 and 5-6, with the ones selected for analysis in this report in boldface type. Table 5-5 lists the RRs and their confidence intervals, along with explanatory footnotes, and Table 5-6 provides information on source and place of exposure and on the adjusted analysis. Because most studies include spousal smoking, and interstudy comparisons may be useful, spousal smoking was the preferred ETS surrogate in all except for LAMW and SOBU. In LAMW, spousal smoking data are limited to cases with adenocarcinoma; in SOBU, the data for cohabitants are separate from data for spousal smoking, and much of the ETS exposure appears to result from the cohabitants. Only data for broader exposure to ETS than spousal smoking alone were collected in BUFF, CHAN, SVEN, and HOLE(Coh).

Table 5-5. Estimated relative risk of lung cancer from spousal ETS by epidemiologic study (crude and adjusted for cofactors)

	Never-smokers	
Case-control	Crude RR[1,2]	Adj. RR[1,2,3]
AKIB	1.52 (0.96, 2.41)	1.5 (1.0, 2.5)
BROW	1.52[4] (0.49, 4.79) 1.82[4,5] (0.45, 7.36)[6]	* 1.68[4,5] (0.39, 6.90)[6]
BUFF	0.81[7] (0.39, 1.66)	*
CHAN	0.75[5] (0.48, 1.19)	*
CORR	2.07[8] (0.94, 4.52)	*
FONT[9]	1.37 (1.10, 1.69) 1.21 (0.94, 1.56) 1.32 (1.08, 1.61)	1.29 (1.03, 1.62) 1.28 (0.98, 1.66) *
GAO	1.19 (0.87, 1.63)	1.34[10,11]
GARF	1.31 (0.93, 1.85)	1.70[12] (0.98, 2.94)[6]
GENG	2.16 (1.21, 3.84)	*
HIRA[13]	1.53[10] (1.10, 2.13)	1.64[10] *
HUMB	2.34 (0.96, 5.69)	2.2 (0.9, 5.5)
INOU	2.55[14] (0.90, 7.20)	2.54[10,15] *
JANE	0.86 (0.57, 1.29)	0.93/0.44[16]

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Table 5-5. (continued)

Case-control	Never-smokers	
	Crude RR[1,2]	Adj. RR[1,2,3]
KABA[17]	0.79 (0.30, 2.04)	*
KALA	1.62[18] (0.99, 2.65) 1.41 (0.78, 2.55)	1.92 (1.02, 3.59)[6] *
KATA	*[19]	*
KOO	1.55 (0.98, 2.44)	1.64
LAMT	1.65 (1.22, 2.22)	*
LAMW	2.51[20] (1.49, 4.23)	*
LEE	1.03 (0.48, 2.20)	0.75/1.60[21]
LIU	0.74 (0.37, 1.48)	0.77 (0.35, 1.68)
PERS	1.28 (0.82, 1.98)	1.2 (0.7, 2.1)[6]
SHIM	1.08[22] (0.70, 1.68)	*
SOBU	1.06[18] (0.79, 1.44) 1.77 (1.29, 2.43)	1.13[18] (0.78, 1.63)[6] 1.57 (1.07, 2.31)[6]
SVEN	1.26[5] (0.65, 2.48)	1.4[5]
TRIC	2.08[23] (1.31, 3.29)	*
WU	1.41[24] (0.63, 3.15)	1.2 (0.6, 2.5)[6]
WUWI	0.79 (0.64, 0.98)	0.7

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Table 5-5. (continued)

Case-control	Never-smokers	
	Crude RR[1,2]	Adj. RR[1,2,3]
BUTL(Coh)	2.45[25]	2.02 (0.48, 8.56)[6]
GARF(Coh)	*	1.17[10] (0.85, 1.61)[6]
HIRA(Coh)	1.38 (1.03, 1.87)	1.61 *
HOLE(Coh)[26]	2.27 (0.40, 12.7)	1.99 (0.24, 16.7)[6]

[1]Parentheses contain 90% confidence limits, unless noted otherwise. When not represented in the original studies, the crude ORs and their confidence limits were calculated (or verified) by the reviewers wherever possible. Boldface indicates values used for analysis in text of this report. Odds ratios are shown for case-control studies; relative risks are shown for cohort studies.
[2]ORs for never-smokers apply to exposure from spousal smoking, unless indicated otherwise.
[3]Calculated by a statistical method that adjusts for other factors (see Table 5-3), but not corrected for smoker misclassification.
[4]Adenocarcinoma only. Data for crude OR values communicated from author (Brownson).
[5]Exposure at home and/or at work.
[6]95% confidence interval.
[7]Exposure to regularly smoking household member(s). Differs slightly from published value of 0.78, wherein 0.5 was added to all exposure cells.
[8]Excludes bronchioalveolar carcinoma. Crude OR with bronchioalveolar carcinoma included is reported to be 1.77, but raw data for calculation of confidence interval are not provided.
[9]The first, second, and third entries are calculated for population controls, colon cancer controls, and both control groups combined, respectively. For adenocarcinoma alone, the corresponding ORs, both crude and adjusted, are higher by 0.15-0.18.
[10]Composite measure formed from categorical data at different exposure levels.
[11]For GAO, data are given as (number of years lived with a smoker, adjusted odds ratio [OR]): (<20, 1.0), (20-29, 1.1), (30-39, 1.3), (40+, 1.7).
[12]Estimate for husband smoking 20 cig. day.
[13]Case-control study nested in the cohort study of Hirayama. OR for ever-smokers is taken from cohort study. This case-control study is not counted in any summary results where HIRA(Coh) is included.
[14]OR reported in study is 2.25, in contrast to the value shown that was reconstructed from the confidence intervals reported in the study; no reply to inquiry addressed to author had been received by press time.
[15]For INOU, data are given as (number of cig./day smoked by husband, adj. OR): (<19, 1.58), (20+, 3.09).
[16]From subject responses/from proxy responses.

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Table 5-5. (continued)

[17]For second KABA study (see addendum in study description of KABA in Appendix A), preliminary unpublished data and analysis based on ETS exposure in adulthood indicate 68% of never-smokers are exposed and OR = 0.90 (90% C.I. = 0.51, 1.58), not dissimilar from the table entry shown.

[18]For the first value, "ETS-exposed" means the spouse smokes; for the second value, "ETS-exposed" means a member of the household other than the spouse smokes.

[19]OR is not defined because number of unexposed subjects is zero for cases or controls.

[20]Table entry is for exposure to smoking spouse, cohabitants, and/or coworkers; includes lung cancers of all cell types. OR for spousal smoking alone is for adenocarcinoma only: 2.01 (90% C.I. = 1.20, 3.37).

[21]From subject responses/from spouse responses.

[22]From crude data, estimated to be: exposed cases 52, exposed controls 91, unexposed cases 38, unexposed controls 72.

[23]Known adenocarcinomas and alveolar carcinomas were excluded, but histological diagnosis was not available for many cases. Data are from Trichopoulos et al. (1983).

[24]Raw data for WU are from Table 11 of Surgeon General's report (U.S. DHHS, 1986). Data apply to adenocarcinoma only.

[25]RR is based on person-years of exposure to spousal smoking. "Prevalence" in those units is 20%.

[26]RR values under never-smoker are for lung cancer mortality. For lung cancer incidence, crude RR is 1.51 (90% C.I. = 0.41, 5.48) and adjusted RR is 1.39 (95% C.I. = 0.29, 6.61).

*Data not available.

Table 5-6. Effect of statistical adjustments for cofactors on risk estimates for passive smoking[1]

Case-control study	Exposure		Crude RR[4]	Adj. RR[4]	Adjustment factor(s)[5]	Adj. technique[6]
	Source[2]	Place[3]				
AKIB	Sp	A	1.52	1.5	A,L,O,V	LR
BROW	Sp	A	1.52	*	*	*
	A	P	1.82	1.68	A,I,O	LR
BUFF	Co	H	0.81	*	*	*
CHAN	A	A	0.75	*	*	*
CORR	Sp	A	2.07[7]	*	*	*
	M(C)	A	1.66[7]	1.36[7]	Sm	R
FONT	Sp	A	1.37[8]	1.29[8]	A,E,I,L,R	LR
	Sp	A	1.21[9]	1.28[9]	A,E,I,L,R	LR
GAO	Sp	A	1.19	1.34[10]	A,E	R
	A	A	*	0.9	A	LR
GARF	Sp	H	1.31	1.70	A,SES,H,Yd	R
GENG	Sp	A	2.16	*	*	*
HIRA	Sp	A	1.53[10]	1.64[10]	A,F,Oh,	S
	Sp	A	1.53	1.50	F	S
HUMB	Sp	A	2.34	2.2	A,R	R
INOU	Sp	A	2.55	2.54[10]	A	S
JANE	Sp	A	0.86	0.93/0.44[11]	A,L,R	M,S
	A(C)	H	*	1.09/2.07[12]	A,R	
KABA	Sp	A	0.79	*	*	*
KALA	Sp	A	1.62	1.92	A,E,Ir	LR
	OC	H	1.41	*	*	*
KOO	Sp	A	1.55	1.64	A,E,B,Yc	LR
	Co	H	1.34	1.68	A,E,B,Yc	LR
LAMT	Sp	A	1.65	*	*	*

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Table 5-6. (continued)

Case-control study	Exposure		Crude RR[4]	Adj. RR[4]	Adjustment factor(s)[5]	Adj. technique[6]
	Source[2]	Place[3]				
LAMW	Sp	*	2.01[13]	*	*	*
	A	*	2.51[14]	*	*	*
LEE	Sp	A	1.3[15]	1.60[15]	A	S
			0.75	0.75		
			[1.03	1.00]		
	Co	H	0.80	0.87[10]	A	S
LIU	Co	A	0.74	0.77	C	LR
PERS	Sp	A	1.28	1.2	A,V	M
	Sp	A	1.28	1.47[10]	A	S
SHIM	Sp	H	1.08	*	*	*
SOBU	Sp	A	1.06	1.13	A,E	S
	OC	A	1.77	1.57	A,E	S
SVEN	A	H,W	1.1/1.8[16]	1.2/2.1[16]	A	S
			(1.26)	(1.4)		
TRIC	Sp	A	2.08	*	*	*
WU	Sp	A	1.41[17]	1.2	A,L	M
					As	LR
WUWI	Sp	P	0.79	0.7	A,E,L	LR
	Co	P	0.78	0.7	A,E,L	LR
BUTL (Coh)	Sp	A	2.45	2.02	A	S
GARF (Coh)	Sp	A	*	1.27/1.10[18]	A	S
				1.17	A,E,L,R,Oh	S
				1.37/1.04[18]		
HIRA (Coh)	Sp	A	1.38	1.61	Ah	S
HOLE (Coh)	Co	A	2.27	1.99	A,SES	S

[1]Values used for inference in this report are shown in boldface.
[2]Source: A = anyone; (C) = childhood; Co = cohabitant(s); M = mother; OC = cohabitant(s) other than spouse; Sp = spouse.
[3]Place: A = anywhere; H = home/household; P = proximity of subjects; W = workplace.
[4]OR for case-control studies; RR for cohort studies.

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Table 5-6. (continued)

[5]Adjustment factors: A = age of subject; Ah = age of husband; As = age started smoking; B = number of live births; C = cooking habits; E = education; F = fish consumption; H = hospital; I = income; Ir = interviewer; L = location; O = occupation of subject; Oh = occupation of husband; R = racial or ethnic group; SES = socioeconomic status; Sm = active smoking; V = vital status; Yc = years since exposure ceased; Yd = year of diagnosis.
[6]LR = logistic regression; R = regression; M = matched analysis; S = stratified.
[7]Bronchioalveolar carcinoma excluded. Spousal smoking OR = 1.77 with bronchioalveolar carcinoma excluded; no corresponding value reported for maternal smoking.
[8]Population controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.52 and 1.47, respectively).
[9]Colon cancer controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.35 and 1.44, respectively).
[10]Composite measure formed from categorical data at different exposure levels.
[11]Cases and controls matched on A, L, and N; first value is from subject; second value is from proxy sources.
[12]1-24 smoker-years/$\geq$ 25 smoker-years.
[13]Adenocarcinoma only.
[14]All cell types.
[15]First value is for smoking information provided by patient's spouse; second value is for information provided by patient herself; third value (in brackets) utilizes available data from either source with subject classified as exposed if either source so indicates.
[16]Exposed at home but not at work or vice versa/exposed both at home and at work followed by weighted average of exposed strata.
[17]Crude OR from Table 11 of Surgeon General's report (U.S. DHHS 1986); note that adjusted OR from WU is not restricted to never-smokers and analysis includes only adenocarcinoma.
[18]Spouse smokes 1-20 cig. per day/spouse smokes $\geq$ 20 cig. per day. The composite RR is 1.17.

*Data not available.

After exposure source and place are taken into account in the choice of RR values in Table 5-6, an adjusted RR is considered preferable to a crude RR unless the study review in Section A.4 indicates a problem with the adjustment procedure. Of the 31 studies, 20 provide both an adjusted and crude RR, where the "adjusted estimate" is based on the author's use of a statistical procedure that takes potential confounding factors into account, usually by stratification or logistic regression. Based on the decision rule just described, our choice of RR is the smaller of the crude and adjusted values in 14 of the 20 studies providing both estimates. In several studies, RR values in addition to those shown in Table 5-6 might be considered (see Table 5-7). They were not found to be the best choices, however, for comparison between studies.

5.2.2. Downward Adjustment to Relative Risk for Smoker Misclassification Bias

There is ample evidence that some percentage of smokers, which differs for current and former smokers, misrepresent themselves as never-smokers (sometimes the wording of a

Table 5-7. Alternative estimates of lung cancer relative risks associated with active and passive smoking

Study	Active/ passive	ETS exposure	Controls exp. (%)	Alternative estimate	Comparison estimate[1]
BUFF[2]	Passive	Household members regularly smoking for 33+ years	71	Crude OR 0.95 (0.38, 2.40)	0.81
FONT[3]	Passive	Spousal smoking, all types	63	Crude OR 1.52[4] (1.19, 1.96)	1.37
				Adj. OR 1.47	1.29
			66	Crude OR 1.35[5] (1.02, 1.80)	1.21
				Adj. OR 1.44	1.28
			64	Crude OR 1.47[6] (1.15, 1.87)	1.32
				No adj. OR	*
HUMB[7]	Passive	Spousal cigarette smoking[7]	57	Crude OR 1.8 (0.6, 5.4)	2.3
				adj. OR 1.7	2.2
KOO[8]	Passive	Home and/or workplace exposure over lifetime[8]	64	Crude OR 1.36 (0.83, 2.21)	1.34
				Adj. OR 1.86	1.64
PERS[9]	Active	N.A.[10]	37[11]	Crude OR 4.2	*
SHIM[12]	Passive	Total household ETS exposure[12]	77	Crude OR 1.36	1.08
BUTL (Coh)	Active	N.A.[10]	14[11]	Adj. RR 4.0[13]	*
HIRA[14] (Coh)	Active	N.A.[10]	44[11]	Adj. RR 3.79	2.67
HOLE[15] (Coh)	Active	N.A.[10]	56[11]	Adj. RR 4.2	*

[1]Nearest equivalent from Tables 5-5 or 5-6.
[2]Values in Tables 5-5 and 5-6 include household smoking for any duration. Lung cancer may have a long latency period, however, so the extended exposure may be of interest.
[3]As in Table 5-5 except for adenocarcinoma alone.
[4]Population controls only.
[5]Colon cancer controls only.
[6]Control groups combined.
[7]Values in Tables 5-5 and 5-6 include spousal smoking of cigars and pipes.
[8]Value in Table 5-6 is for household cohabitant smoke exposure during adulthood.

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Table 5-7. (continued)

[9]Estimate is based on papers by Cederlöf et al. (1975) and Floderus et al. (1988) describing larger populations on which Pershagen study was based.
[10]Not applicable because alternative estimate is for active smoking.
[11]Percentage ever-smokers.
[12]Composite estimate from crude ORs for exposure from husband, parents, and father-in-law. Values in Tables 5-5 and 5-6 consider only spousal smoke exposure.
[13]Rough estimate based on data in Fraser et al. (1991). The prevalence of female ever-smoking is estimated from KALA and TRIC studies, which were conducted in similar conservative societies.
[14]Compares active smokers with never-smokers unexposed to ETS, thus providing a reference group more truly unexposed to tobacco smoke. The value in Table 5-5 is the more conventional comparison of ever-smokers with never-smokers, regardless of passive smoking status.
[15]Estimate is from adjusted RR for both sexes combined with assumption that female RR is 75% of male RR.

*Data not available.

questionnaire may not be explicit enough to distinguish former smokers from never-smokers) (see Appendix B). It has been argued that the resultant misclassification of some smokers as nonsmokers produces an upward bias in the observed relative risk for lung cancer from ETS exposure (i.e., the observed RR is too large). The essence of the supporting argument is based on smoking concordance between husband and wife--a smoker is more likely than a nonsmoker to have been married to a smoker. Consequently, the smoker misclassified as a nonsmoker is more likely to be in the ETS-exposed classification as well. Because smoking causes lung cancer, a misclassified smoker has a greater chance of being a lung cancer case than a nonsmoker. The net effect is that an observed association between ETS exposure and lung cancer among people who claim to be never-smokers may be partially explainable by current or former active smoking by some subjects.

The potential for bias due to misreported smoking habits appears to have been noted first by Lee (see discussion in Lehnert, 1984), and he emphasizes it in several articles (e.g., Lee, 1986, 1987a,b). In Lee, 1987b, it is argued that smoker misclassification may explain the entire excess lung cancer risk observed in self-reported never-smokers in epidemiologic studies. Lee's estimates of bias due to smoker misclassification appear to be overstated, however, for reasons discussed in Appendix B.

The NRC report on ETS (1986) devotes considerable attention to the type of adjustment for smoker misclassification bias. It follows the construct of Wald and coworkers, as described in Wald et al., 1986; Wald was the author of this section in the 1986 NRC report. An illustrative diagram for the implicit true relative risk of lung cancer from exposure to ETS in women from